Human Molecular Genetics, 2011, Vol. 20, Review Issue 2 ***R132–R141***
doi:10.1093/hmg/ddr349
Advance Access published on August 9, 2011

Direct-to-consumer personalized genomic testing

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Received July 21, 2011; Revised and Accepted August 4, 2011

Over the past 18 months, there have been notable developments in the direct-to-consumer (DTC) genomic testing arena, in particular with regard to issues surrounding governmental regulation in the USA. While commentaries continue to proliferate on this topic, actual empirical research remains relatively scant. In terms of DTC genomic testing for disease susceptibility, most of the research has centered on uptake, perceptions and attitudes toward testing among health care professionals and consumers. Only a few available studies have examined actual behavioral response among consumers, and we are not aware of any studies that have examined response to DTC genetic testing for ancestry or for drug response. We propose that further research in this area is desperately needed, despite challenges in designing appropriate studies given the rapid pace at which the field is evolving. Ultimately, DTC genomic testing for common markers and conditions is only a precursor to the eventual cost-effectiveness and wide availability of whole genome sequencing of individuals, although it remains unclear whether DTC genomic information will still be attainable. Either way, however, current knowledge needs to be extended and enhanced with respect to the delivery, impact and use of increasingly accurate and comprehensive individualized genomic data.

Over the past few years, there has been a flurry of activity in the direct-to-consumer (DTC) genetic testing space, an area of genomics that has been fraught with controversy. As the number of companies and number of tests offered by each company have proliferated (1), so, too, have efforts aimed at increased governmental regulation of this industry, especially in the USA (2,3). Over the past year, we have also seen actual empirical data start to emerge on both perceptions of and attitudes toward DTC genetic testing, as well as on psychological and behavioral responses to testing. Our review of available studies suggests, however, that more work in this area is desperately needed even though there are challenges with respect to the design and timely execution of such studies. For instance, there are no available studies on long-term follow-up of individuals who have undergone DTC genomic testing for disease susceptibility, nor any studies on response to testing for genetic ancestry or pharmacogenomic testing. Further, there are still open questions with respect to the consistency of disease risk estimates provided by different DTC companies (4,5), as well as related questions surrounding the clinical validity and clinical utility of tests that are offered.

In this review, we briefly discuss the pros and cons of DTC personalized genomic testing and describe the current landscape of the DTC genetic testing market. We also review important events over the past year, which have been aimed at issues surrounding US governmental regulation of DTC testing. We then delineate ongoing large-scale research initiatives that aim to inform relevant issues pertaining to DTC genomic testing, as well as currently available research findings in this area. Finally, we comment on topics that we believe are 'on the horizon' in this area, including DTC genomic testing of children and adolescents, as well as the potential for affordable DTC whole genome sequencing (WGS). We suggest that DTC genomic testing for common markers and conditions is only a precursor to the eventual cost-effectiveness and wide availability of WGS of individuals, although whether or not this information will remain directly available to consumers is still an open question.

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PROS, CONS AND THE CURRENT LANDSCAPE OF DTC GENOMIC TESTING

As of May 2010, there were >30 DTC genetic testing companies that collectively offered >400 health-related tests (1), and these numbers appear to be on the rise. These tests can, by definition, be purchased by consumers online. The fees for different tests have typically ranged from $99 to over $2000, and testing does not require the involvement of a health-care provider, although some companies are now imposing such a requirement [e.g. pathway genomics (6)]. There are a range of types of genetic tests that are currently offered DTC, as well as wide variation with respect to the extent to which each company uses the scientific literature to support their decisions concerning which tests they offer. This review will, for the most part, focus on tests where results are provided for multiple common genetic markers conferring susceptibilities for multiple common health conditions and traits. These tests are based on high-throughput genome-wide genotyping technologies and findings from genome-wide association studies (7). Starting in late 2007, a number of companies began offering such testing, including 23andMe (8), Navigenics (9), deCODE (10) and in 2008, Pathway Genomics (6).

This type of testing has been highly controversial. Those opposed to it argue that it has limited value given the small relative risks contributed by common genetic variants and the fact that most variants identified to date only account for a small fraction of the genetic variance of any one disease. There is also evidence that the risk estimates provided across companies are inconsistent (4,5,11,12), primarily due to the use of different single nucleotide polymorphisms (SNPs) and risk prediction algorithms. For the most part, the various tests offered also currently lack demonstrated clinical validity and utility (13,14). Other criticisms are that consumers may be confused by their results, or experience anxiety related to premature estimates of high risk, which could result in the pursuit of expensive and unnecessary medical interventions (15). Alternatively, they may be falsely reassured by estimates of low risk and fail to take appropriate preventative measures. On this point, several professional organizations (16–18), including the National Society of Genetic Counselors (19), American College of Medical Genetics (20) and American Medical Association (AMA) (21), have put forth position statements indicating that genetic testing should involve a health-care provider. Other concerns include the possibility of discrimination if privacy is not maintained and the exacerbation of existing health disparities related to the costs of testing and inequitable access for different groups of individuals.

On the other hand, proponents of DTC genomic testing argue that there is public interest in genomic information and that it is overly paternalistic to deny individuals access to information about their own bodies. It is also proposed that direct access to genomic testing may empower consumers to educate themselves, as well as to make proactive decisions about their own health, such as decisions to engage in lifestyle behavioral change efforts aimed at disease risk reduction. In this regard, genomic information is thought by some to be inherently more powerful relative to other types of non-genetic risk information, a notion commonly referred to as 'genetic exceptionalism' (22). Some also assert that DTC genetic testing may, somewhat counter-intuitively, be a viable alternative for individuals who are fearful of genetic discrimination and insurance loss resulting from testing through a health-care provider with the results documented in medical records (23). Overall, these factors have prompted countless commentaries on these and other related topics including, but not limited to, the risks and need (or not) for regulation of DTC testing (24–33), the impact of DTC testing on consumers (34–37), physicians and the healthcare system (15,38), the appropriateness and impact of disease-specific testing (39–41) and implications for genomic research (42–44).

Table 1. Recent timeline of DTC genetic testing events

Year	Month	Event
2010	March	NIH announced creation of Genetic Testing Registry to be launched in 2011
	May	Pathway Genomics announced Walgreens partnership to sell genetic testing kit at over 6000 retail stores
		FDA notified Pathway that kit appeared to meet criteria for medical device, and thus required FDA approval
	June	FDA sends similar letter to five other companies (Knome, Navigenics, deCODE, 23andMe, Illumina)
	July	FDA sends similar letter to 15 additional DTC companies
		FDA holds public meeting on how the Agency should regulate LDTs
		Congressional Committee holds hearing on 'DTC Genetic Testing and Consequences to the Public Health'
		GAO report on DTC genetic testing and 'sting' operation released
2011	February	AMA sends letter to FDA suggesting that all genetic testing be done under the guidance of a physician
	March	FDA holds meeting to discuss the regulation of DTC genetic testing (Molecular and Clinical Genetics Panel)
	May	FDA sends letter to three additional DTC companies

While there has been a lively debate over these issues since the above-mentioned DTC genomic testing companies came on the scene roughly 4 years ago, over the past 18 months, issues around US governmental regulation have come to a head (Table 1, timeline). Specifically, consumer genomic testing came under fire in May 2010 when Pathway Genomics announced a partnership with Walgreens Drug Stores in which they planned to sell their DNA saliva kits on the shelves at >6000 retail stores nationwide (45). This would have marked the first time that the sale of these tests moved from internet commerce to retail availability. This led the US Food and Drug Administration (FDA) to question the federal regulatory approval of the tests offered by all of the primary DTC genomic testing companies (6,8–10,46) and another service provider (47).

In part prompted by these events, the FDA held a public meeting in July 2010 to help determine how regulation of so-called laboratory developed tests (LDTs) should proceed. That same month there was a Congressional Committee hearing to evaluate the 'public health consequences' of DTC genomic testing (48), as well as the release of a new report assembled by the General Accounting Office (GAO) in which a 'sting' operation targeted at DTC genomic testing companies was unveiled (5). The report presented findings, which suggested that some of the companies not only produced inaccurate test results, but also engaged in deceptive

marketing practices. Notably, this was not the first such report on DTC testing issued by the GAO (49). Discussion regarding regulation continued when, in February 2011, the AMA sent a letter to the FDA strongly suggesting that all genetic testing be pursued under the guidance of a physician (21), which some have suggested is ironic given that most physicians report a lack of knowledge in the area of genomic medicine (50,51). This was done in advance of a March meeting where a special panel was convened to gather information on, and to evaluate the benefits and harms of, DTC genomic testing in order to inform the FDA (3). While, to our knowledge, no firm decisions have been made yet regarding the regulatory process for DTC genomic testing, the sense among many is that soon such tests may only be available through one's physician.

In parallel, the National Institutes of Health (NIH) has responded to increasing concerns over the need for transparency about genetic testing and the potential for misinterpretation of results by initiating the development of a Genetic Testing Registry (GTR) (52). The GTR will be a publically available, online database that provides information addressing the availability, clinical validity and clinical utility of genetic tests. The goal of this effort is to better equip physicians and consumers to determine the appropriateness of specific genetic tests (53). Information in the registry will be voluntarily provided by genetic testing companies, and it is projected to become available in late 2011.

RESEARCH INITIATIVES TO INFORM DTC GENOMIC TESTING FOR COMMON DISEASES

The controversies around DTC genomic testing have been complicated by a lack of empirical, prospective data. To begin to bridge this gap, we know of three large-scale research studies that have been initiated, including the Coriell Personalized Medicine Collaborative (CPMC) (54,55), the Multiplex Initiative (56–58) and an effort from our own institute, the Scripps Genomic Health Initiative (SGHI) (59,60). While all three studies are unique in several respects, they share a notable strength, which is the enrollment of large sample sizes. Previous studies on the behavioral and psychological response to testing for single-gene conditions have been limited in this respect (61). We briefly describe each of these initiatives below, and then in the following section, review specific research findings that have emerged from these efforts, in addition to other published studies.

Coriell Personalized Medicine Collaborative

The CPMC (54) is a prospective observational cohort study designed to assess the impact of multiplex genomic testing and return-of-results on health behaviors. A recent paper by Keller and colleagues (55) indicated that over 4000 individuals have been enrolled in the CPMC community cohort to date. Participants provide medical history information via a web-based survey, and DNA is tested for at least 16 health conditions. Participants receive an email request to complete a follow-up health behavior outcome survey every 3 and 12 months after viewing a risk report. Thus far, customized risk results (55) have been disclosed for a subset of six conditions; however, there are currently no published data of which we are aware that have reported on the behavioral response of individuals to testing.

Multiplex Initiative

The Multiplex Initiative was launched in 2006 and is led by scientists at the National Human Genome Research Institute (NHGRI) (56). This initiative is also a prospective, observational study, and is designed to answer questions about the characteristics of individuals who, when offered free susceptibility testing for multiple common diseases, have interest in being tested (62). Particular strengths of this study are that participants were drawn from a known sampling frame of individuals enrolled in a large health system and health maintenance organization, and groups traditionally under-represented in research were over-sampled. The genetic test offered includes 15 genetic variants that confer risk for eight common health conditions (63). Published reports to date indicate that the total number of individuals who completed an initial survey and considered undergoing testing was 612, which was 14% of the surveyed sample; of these, 266 provided written consent and had blood drawn for testing (64). The behavioral responses of those participants who underwent testing are assessed via a 3-month follow-up telephone survey. Although we are not aware of any published reports on response to testing, there have been a number of reports that have evaluated characteristics associated with interest in multiplex testing and the decision to get tested (57).

Scripps Genomic Health Initiative

The SGHI is also a prospective, longitudinal, cohort study designed to assess response to DTC genomic testing. The study was initiated in October 2008. Over 4000 individuals were enrolled in the study (59), and roughly half completed an initial follow-up assessment administered at 3 months post-testing (60). Although similar in some respects to the previous two initiatives, the SGHI possesses some unique features, including the fact that SGHI participants purchased a commercially available DTC genomic test [the Navigenics Health-Compass (9)]. Thus, in many ways, participants can be thought of as reflecting 'real' consumers of DTC genomic testing, and indeed, characterization of the sample has revealed that it is largely representative of the current population of consumers of DTC genomic tests (60). Therefore, of all of these initiatives, the SGHI would seem to most closely mirror the current realities of how DTC genomic tests are currently being offered to the public. In the SGHI, participants were administered baseline, as well as 3- and 12-month follow-up web-based health assessments focusing on surveillance/health screening behaviors, lifestyle (i.e. diet and exercise) and psychological functioning. Reports on both the baseline characteristics and perceptions of the sample (59), as well as on the response of participants to testing (60) have been published.

It is worth mentioning that other initiatives, while not focused on multiplex genetic testing, have helped to inform some research questions related to DTC genomic testing and

return of genetic susceptibility risk estimates. One notable example is the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) study in which adult children of individuals with Alzheimer's disease (AD) are offered testing for the apolipoprotein epsilon 4 (*APOE-ε4*) genotype, which confers susceptibility to AD. This study has shown minimal psychological impact of testing (65), and some preliminary evidence of moderate behavioral impact (66). Smaller scale studies on the clinical (67) as well as behavioral impact (58,68,69) of genetic testing for common susceptibility variants have also been done. Furthermore, a search of the NIH's database of currently funded projects (70) using the search term direct-to-consumer reveals 17 matches, including study topics ranging from attitudes and experiences of early adopters of personalized genomics to the impact of DTC genetic testing on policy development. This suggests that additional research to inform this controversial area of genomics may soon start to emerge.

RESEARCH FINDINGS TO DATE CONCERNING DTC GENOMIC TESTING

We searched the empirical and qualitative research literatures for studies that pertain to, or were designed to inform, DTC genomic testing. Our search produced a few noteworthy findings. First, in general, although many commentaries have been published on this topic, there are few actual research studies (Table 2). Secondly, very few studies have been published to date that address what is a primary issue in DTC genomic testing, which is how consumers interpret, understand and respond to test results. In fact, a published report from our own SGHI study is the only study of which we are aware that has addressed this question in a large cohort (60). Findings from this study indicated minimal impacts of testing on participants, including a lack of psychological harm. The other main finding was that respondents reported the intention to undergo specific clinical screening tests with greater frequency, which correlated with the pattern of disease risk results that were disclosed. With the exception of two published case studies of individuals who underwent DTC genomic testing (23,71), we found only one other study that has evaluated response to multiplex genomic testing, which was a small-sample study of individuals with advanced training in genetics (72) (Table 2).

The other studies identified seem to reflect a few main themes, including (i) awareness of DTC genomic testing; (ii) demographics, interest and attitudes and perceptions among potential consumers and health-care providers; (iii) communication of genomic information and genomic risk; and (iv) the impact of testing on the health-care system. In terms of public awareness, findings to date seem to suggest that while some segments of the population (e.g. well-educated, internet-savvy individuals) are quite aware of DTC genomic tests, the majority of the general population is not (73–76). Consistent with this, one study published in 2010 estimated that the overall demand for DTC genomic tests at the time of the study was likely small, and thus the impact on health systems was likely to also be minimal (77). Likewise, two studies that have actually tried to assess the impact of DTC genomic testing on the number of health-care referrals have also drawn similar conclusions (78,79). Importantly, all of these studies only reflect the landscape of DTC genomic testing at a given point in time and cannot necessarily speak to future demand.

In terms of uptake of testing by different groups, early studies suggest that women, individuals of Caucasian background, and highly educated individuals are most likely to undergo testing (54,59,62). Further, those interested in testing primarily cite curiosity as the reason (51,80,81) or a belief that it is important to learn about genetics (57). They also often indicate their intention to include their physician in the process (80,82). Also, interestingly, even those who decide or intend to undergo testing still have concerns about the process, most notably concerns related to confidentiality (51,59). A few other studies have also examined communication patterns around delivery of DTC genomic test results. This work suggests that individuals can find web-based information on multiplex genomic testing to be helpful in their decision-making around whether or not to be tested (83); however, a content analysis of 29 actual DTC websites found that overall, the sites demanded high literacy levels, suggesting that many users may struggle to find and understand important information (84).

DTC PHARMACOGENOMIC AND ANCESTRY TESTING

Two other prominent types of tests offered by many DTC genomic testing companies are pharmacogenomic tests and testing for ancestry or one's 'geographical origins'. Pharmacogenomic markers and associations arguably represent an area of genomics that may in fact be most ready for clinical translation (85), although as with DTC genomic disease susceptibility testing, ethical and social issues have been raised (86,87). Table 3 shows pharmacogenomic tests offered as of June 2011 by the three primary DTC genomic testing companies. In regards to ancestry testing, Royal *et al.* (88) indicated that at the time of publication, there were ~40 companies in various countries that were providing genetic ancestry testing to the public. Although there are population-specific differences in disease and drug response (89) and thus ancestry testing could theoretically inform health-related issues, it has been suggested that most scientists and consumers view these tests as merely recreational (90). Notably, we know of no studies that have evaluated consumer response to either pharmacogenomic or ancestry testing. Questions such as whether or not consumers bring their 'medications' test results to their physician, or whether ancestry testing is impactful in terms of an individual's self-concept, loom large. In the future, we hope to be able to speak to such questions through analysis of relevant data we have collected as part of our SGHI study. Further, several companies are continually developing new tests, including tests that take into account an individual's specific phenotypic characteristics (e.g. see the 'Pathway Fit' test, a nutrigenomic test currently offered by Pathway Genomics: https://www.pathway.com/dna-reports/pathway-fit).

Table 2. Recent empirical and qualitative research informing multiplex DTC genomic testing for common disease

Research focus	Author and year	Method/subject group	Aims and findings	Reference
Awareness, testing market and media	Kolor *et al.*, 2009	Results of two national surveys (HealthStyles and DocStyles)	Used 2008 DocStyles and HealthStyles national surveys to examine awareness of DTC genomic tests among health-care providers ($n = 1880$) and individuals/consumers ($n = 5399$). Found that 22% of individuals were aware of tests and 0.3% had used them; of those that had tested, two-thirds had shared results with a physician. Alternatively, 42% of health-care providers were aware of tests, and of those, 15% reported having at least one patient who sought to discuss the test results	(74)
	Wright and Gregory-Jones, 2010	Used Compete.com to assess internet traffic on DTC websites	Assessed internet traffic on websites of the three most prominent DTC genomic test companies as a proxy for commercial activity. Found 23andMe to lead with an average of 78% of the unique visitors per month in 2009. Overall, found the demand for DTC genomic tests for common disease susceptibility to be small and thus the likely impact on health systems to also be minimal	(77)
	Lynch *et al.*, 2011	Lexis-Nexis search for DTC genetic test news stories from 2006 to 2009	Assessed themes presented by US news media regarding DTC genetic testing. Identified 92 news stories. Found that stories displayed moderate genetic determinism and were neutral about validity and utility. Identified physicians and DTC companies as groups most likely to violate privacy. Overall, found that a broad range of views were presented	(111)
Uptake, interest, attitudes and perceptions	McBride *et al.*, 2009	Adults aged 25–40 years enrolled in the Multiplex Initiative	Goal was to determine what psychological and behavioral factors predict who is likely to seek SNP-based genetic tests for multiple common health conditions. Only a third of those offered free testing logged on to a study website to review the relevant information ($n = 612$), and less than half of this group elected to undergo testing ($n = 266$). Individuals who believed it important to learn about genetics, were confident they could understand genetics, and self-reported the greatest number of health habits to change were most likely to get tested	(57)
	McGuire *et al.*, 2009	Online survey of social networking users	Survey of 1087 social networkers (i.e. likely 'early adopters') indicated that 64% would consider using DTC genomic testing, 30% would not and 6% had already been tested. Of those who would consider testing, 78% would ask their physician for assistance with interpretation, and 54% would consider using DTC testing for their child	(75)
	Bloss *et al.*, 2010	Adult DTC genomic test consumers aged 18–85 enrolled in the SGHI	Among a sample of 3640 DTC genomic test consumers, found that roughly half still reported concerns about undergoing testing. Specific concerns endorsed included concerns related to privacy of results and the quality and reliability of the data. Concerns were also found to vary as a function of demographic characteristics, including age, gender, occupation and education, as well as level of trait anxiety	(59)
	Keller *et al.*, 2010	Adults enrolled in the community cohort of the CPMC	The CPMC is composed of three cohorts: community, cancer and chronic disease. Between December 2007 and December 2009, the community cohort reached 4372 individuals enrolled. Of those enrolled, 2809 have completed a demographic questionnaire, which shows that the sample is predominately female (63%), well educated and Caucasian (92%); in addition, 26% are health-care professionals	(54)
	Gollust *et al.*, 2011	Adults registered to attend an enrollment event for the CPMC	Among 369 individuals registered for a CPMC event between March 2009 and April 2010, motivations and perceptions of genomic testing were assessed. These 'likely early adopters' indicated that they were motivated to participate for their own curiosity and to find out disease risks to improve health. In addition, fewer than 10% expressed deterministic perspectives about genetic risk, and 92% intended to share their results with physicians	(80)
	Hensley Alford *et al.*, 2011	Adults aged 25–40 years enrolled in the Multiplex Initiative	Aim was to evaluate, using a population-based sample of healthy adults, whether gender, race and education influenced interest in and the decision to undergo multiplex genetic susceptibility testing. Found that African Americans were less likely to participate in the multiplex genetic susceptibility test and those from higher education neighborhoods were more likely to participate	(62)
	Sweeny and Legg, 2011	Adults aged 19 to 78 years recruited via web advertisements	Participants ($n = 99$) read positive, negative, or positive and negative information about DTC genomic testing. Found that the information types people received predicted their intentions about whether or not to undergo testing. Authors suggest this could have implications for designing interventions to encourage or discourage the use of DTC genomic tests	(112)
	Ormond *et al.*, 2011	First-year medical and graduate students	Students were surveyed before and after ($n = 31$) a graduate level genetics course to determine attitudes toward personal genomic testing for both physicians and consumers. After the course, students were less likely to believe in the usefulness of genotyping information; a slight majority of the students were and remained interested in undergoing genotyping themselves, but cited curiosity as the primary reason; 50% of students expressed concern about the confidentiality of the results	(51)
	Su *et al.*, 2011	Content analysis of DTC test users' posts on internet blogs and websites	Through analysis of internet blog and DTC genomic test website posts, the personal stories of roughly 47 individuals who had undergone DTC genome testing were assessed. Results indicated five major sets of motivations and expectations towards DTC genomic testing, including (i) health, (ii) curiosity and fascination, (iii) genealogy, (iv) contributing to research and (v) recreation	(81)
	Wilde *et al.*, 2011	Population-based survey of community-dwelling adults	Survey of 1046 individuals found strong interest in predictive testing for susceptibility to depression. After considering the benefits and disadvantages of testing, there was greater interest in seeking testing through a physician (63%) versus DTC (40%)	(82)

Communication of genomic information	Lachance *et al.*, 2010	Content analysis of health-related DTC genetic testing websites	Analysis of 29 websites found average reading level was grade 15. Most sites presented health conditions, some markers for which they tested, the benefits of testing and the relevant privacy policy; fewer cited the scientific literature, explained test limitations or explained technical terms consistently. Concluded that many users would struggle to find and understand important information given wide variation in informational content, literacy demands and usability	(84)
	Kaphingst *et al.*, 2010	Adults aged 25–40 years enrolled in the Multiplex Initiative	Aim was to inform concerns regarding whether individuals offered genomic testing DTC can make informed decisions about testing when guided by online decision aids. Participants ($n = 526$) who visited the Multiplex Initiative study website viewed 2.9 of the 4 pages introducing the multiplex test, 2.2 of the 8 pages describing the health conditions and 3.2 of the 15 pages describing the genes. For each page viewed, participants were more likely to describe their decision-making as 'easy'	(83)
	Leighton *et al.*, 2011	Social networkers and genetic counselors	Online survey that included four sample DTC genetic test result profiles was posted on Facebook. Social networkers ($n = 145$) and genetic counselors ($n = 171$) completed the survey. Results showed that the social networkers believed the results in all four scenarios to be more helpful relative to the genetic counselors. The social networkers rated the results as easy to understand, but occasionally misinterpreted them	(113)
Consumer impact of genomic testing	O'Daniel *et al.*, 2010	Individuals with advanced training in genetics (The Duke Personal Variome Project)	A total of 14 participants received individual reports of estimated genomic ancestry, genotype data and reported disease associations at no cost. Emotional, cognitive and health behavioral impact was assessed through one-on-one interviews administered pre- and post-testing. Results suggested high interest before and immediately following testing, but a decline in interest with time. Participants deferred to family history-based risks when genomic risks were inconsistent with this, and there was relatively low uptake of health behavior change	(72)
	Bloss *et al.*, 2011	Adult DTC genomic test consumers aged 19–85 enrolled in the SGHI	Evaluated the impact of testing with the Navigenics HealthCompass among a cohort of 2037 consumers who completed follow-up assessment. Analyses showed no significant impact on anxiety symptoms, dietary fat intake or exercise behavior. Test-related distress was positively correlated with the average estimated lifetime risk among all the assessed conditions, but over 90% of participants indicated no test-related distress. There was also no significant increase in the actual use of health screening tests; however, participants reported the intention to increase the frequency of screening in the future	(60)
	Austin and Hegele, 2011	Case study	Patient (52-year-old male) underwent DTC genomic testing with 23andMe. In terms of risk for cardiovascular disease, genotyping suggested decreased risk, versus family history, which suggested increased risk. Underscores the importance of an understanding of DTC genomic test limitations among both consumers and physicians	(71)
	Roberts *et al.*, 2011	Case study	Patient from large family affected with Lynch syndrome in which there is a known mutation in *MSH2*. Patient was aware that clinical genetic testing for the familial mutation was available, but was concerned that if the result was positive, he/she would lose or be unable to afford health insurance. Instead underwent testing with 23andMe, and was able to determine, with the help of a medical geneticist, that he/she was in fact a carrier	(23)
Health-care impact of genomic testing	Hock *et al.*, 2011	Members of the National Society of Genetic Counselors	Members ($n = 312$) completed a web-based survey in 2008. A total of 83% had two or fewer inquiries about DTC genetic testing, and 14% had received requests for test interpretation or discussion. Fifty-one percent thought testing should be limited to a clinical setting, and more than 70% would consider testing for patients who have concerns about genetic discrimination	(78)
	Giovanni *et al.*, 2010	Members of three different groups of genetics professionals	Surveyed 133 members across three professional groups, including the National Society of Genetic Counselors, the list serve of the Adult Genetics Special Interest Group and the American College of Medical Genetics. Respondents described 22 cases of clinical interactions following DTC genetic testing. Most (59.1%) were self-referred, but 31.8% were physician-referred; about half who saw patients after testing judged the testing to be clinically useful	(79)
Pediatric DTC genomic testing	Tercyak *et al.*, 2011	Parents enrolled in the Multiplex Initiative	Parents ($n = 219$) who were offered multiplex testing for eight common health conditions themselves were surveyed regarding their attitudes and beliefs about having their child tested. Respondents viewed the benefits of pediatric testing to outweigh the risks and were moderately interested in testing	(103)
	Howard *et al.*, 2011	DTC genetic testing companies	Surveyed 37 DTC genetic testing companies between December 2009 and April 2010 regarding their policies for testing children. Of the 13 companies that responded, found that a majority do perform testing in minors. Authors emphasize that companies testing children for adult-onset diseases for which there are no established therapeutic or preventative strategies are acting in contradiction of established professional guidelines	(101)

CPMC, Coriell Personalized Medicine Collaborative; SGHI, Scripps Genomic Health Initiative.

Table 3. Pharmacogenomic tests offered by three primary DTC genomic testing companies as of June 2011

Drug/health issue	Indications	Pathway Genomics	Navigenics	23andMe
Abacavir hypersensitivity	HIV treatment	x	x	x
Aminoglycoside-induced ototoxicity	Antibiotic for treatment of severe bacterial infections	x		
Antidepressant response	Depression, anxiety			x
Azathiopurine/6-Mercaptopurine	Anti-inflammatory, treatment of autoimmune disorders or cancer		x	
Beta-blockers	Treat high blood pressure, irregular heartbeat,		x	x
Carbamazepine	Epilepsy, bipolar disorder	x	x	
Clopidogrel efficacy	Prevent blood clots	x	x	x
Estrogen-containing medications	Oral contraceptives, HRT	x		x
Floxacillin toxicity	Antibiotic used for staphylococcal infections		x	x
Fluorouracil toxicity	Chemotherapy drug used to treat cancer		x	x
Interferon beta response	Multiple sclerosis treatment			x
Irinotecan	Chemotherapy drug to treat colorectal cancer		x	
Lumiracoxib side effects	Treatment of acute pain and symptoms of osteoarthritis			x
Metformin response	Treat type 2 diabetes			x
Methotrexate toxicity	Antimetabolite/antifolate for cancer/autoimmune disease	x		
Naltrexone response	Alcohol and heroin addiction			x
PEG-IFNalpha/RBV response	Hepatitis C treatment			x
PONV reactions	General anesthesia			x
Pseudocholinesterase deficiency	Stop skeletal muscle contractions; used as part of anesthesia		x	x
Simvastatin/Pravastatin response	Lower cholesterol, stroke prevention	x	x	
Simvastatin-induced myopathy	Lower cholesterol, stroke prevention	x	x	x
Tamoxifen response	Treatment and prevention of breast cancer	x		
Warfarin sensitivity	Blood thinner	x	x	x

DTC GENOMICS AND RESEARCH PARTICIPATION

An interesting outgrowth of commercial DTC genomic testing is that some companies offering such testing are, in parallel, building their own databases and conducting genetic research on the basis of the data obtained from their customers (44). 23andMe (8) is likely the most prominent example of a company operating in this way, and from the time they opened their doors, they have embraced a business model that has clearly reflected the intention to promote and perform research (91). This model of 'crowdsourcing' genetic disease research (43,92) in many ways stands in opposition to conventional models and thus has been an additional source of controversy with respect to DTC genomic testing (93). In 2010, researchers affiliated with 23andMe published the first report to emerge from what they termed their 'web-based, participant-driven' genetic studies (94) in which they identified new genetic trait associations, as well as replicated several previously reported findings. Their second study, focused on the genetic basis of Parkinson's disease, was published in 2011, identified two novel loci and represented a meaningful contribution to the field (95). The success of these studies as well as other similar initiatives [e.g. for ancestry, the National Geographic 'Genographic' project (96)] suggests that this model of research participation, powered by large sample sizes that are hard to come by but a necessity for genomic research, may be both fruitful in terms of genetic discovery, as well as less costly compared with more traditional research mechanisms.

ISSUES ON THE DTC GENOMIC TESTING HORIZON

Since the emergence of the first DTC genomic testing companies in 2007, this area of genomics has been evolving rapidly and has been the subject of much intense debate. Anecdotally, at least, there is evidence that public interest in genomics appears to be increasing [e.g. the availability of personal genomics mobile 'apps' such as DYI Genomics (92) and the Genome Wowser (97), the popularity of genomics websites such as www.snpedia.com]. Therefore, it is likely that the important issues raised with respect to the public's level of access to genomic testing will remain a priority area for current and future research.

We concur with others in the field regarding the need for further and ongoing thoughtful evaluation of the potential harms to consumers associated with DTC genomic testing (98). Although we offer that our initial analysis of this issue in the context of our SGHI study suggests that adverse anxiety reactions, at least, may be minimal (60), additional studies are needed. However, given this preliminary evidence coupled with similar findings from studies of risk-disclosure for single-gene conditions (61), we would urge policy makers to proceed cautiously in any effort to limit the ability of consumers to access this information. While some level of regulation is likely appropriate, over-regulating may serve to stifle innovation in this burgeoning area of scientific translation (99).

In terms of future work, we propose that there are a few particularly relevant areas of DTC genomic testing that would greatly benefit from further research. These include, but are not limited to, the following: (i) research on consumer response to both DTC pharmacogenomic testing, as well as ancestry testing; (ii) issues surrounding the need for physician education in the area of genomic medicine (50,51,100), as well as studies on the best and most efficient ways of presenting individual-level genomic data to health-care providers; (iii) the possible DTC testing of minors (101), especially given evidence that younger individuals may be most amenable to adopting or changing risk-reducing lifestyle habits (102) and that parents may find testing to be beneficial (103) (Table 3); (iv) the need for research on the potential

development of effective preventative lifestyle behavioral interventions that leverage genomic information and 'feedback loops' (104); (v) research to better elucidate how genomic discoveries and information can be combined with other emerging health-related technologies, such as wireless sensors, to improve patient care and disease prevention (105); and (vi) finally, issues related to study design in the context of DTC research that has been pursued to date, including the limits associated with certain designs (e.g. studies that lack a control group) and alternative designs for testing certain hypotheses. While we propose these as important avenues of inquiry in this space, we also note the difficulties associated with pursuing research in this area. Specifically, the rapid pace at which the field (in particular the technology) is evolving poses challenges in terms of designing (as well as obtaining funding for) studies that will, once completed, produce findings relevant to the behavioral and psychosocial milieu of DTC genomic testing at that future point in time.

Ultimately, the era of genome-wide scanning can be considered only a segue to WGS. This is especially true as the costs for the latter have been ratcheting down at a rate far beyond projections, although we note that cost is not the primary bottleneck to delivery of personalized genomic information. One company that offers WGS to 'private clients' recently announced provision of their services for research purposes for $<$\$5000 per genome (106). There has also been media coverage of high-profile celebrities obtaining such testing (107), as well as emerging evidence that sequencing strategies for medical purposes is reaping early rewards in terms of the diagnosis and effective treatment of rare diseases (108–110).

In terms of direct access to genomic testing for consumers, we believe that the 'democratization of DNA' that has already been initiated is important to preserve. Individuals and patients should have a right to have their DNA analyzed if they can be assured that this is being done with the highest level of accuracy and with defined limits regarding how the data can be interpreted. In particular, the notion that individuals would be better off if genomic testing were only available through a physician seems flawed given the well-documented lack of physician education and knowledge in genomics (50). Notwithstanding these points, it remains unclear whether or not genomic information (whether it be SNP- or sequence-based) will remain available to consumers without the involvement of a health-care provider. Either way, however, current knowledge needs to be extended and enhanced with respect to the delivery, impact and use of increasingly accurate and comprehensive individualized genomic data.

Conflict of Interest statement. None declared.

FUNDING

This work was supported in part by a National Institutes of Health/National Human Genome Research Institute R21 grant (grant number 1R21HG005747-01 to C.S.B.), a National Institutes of Health/National Center for Research Resources flagship Clinical and Translational Science Award grant (grant number 1UL1RR025774-01 to E.J.T.) and Scripps Genomic Medicine Division of Scripps Health.

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