ANNUAL REVIEWS

Annual Review of Medicine

Direct-to-Consumer Genetic Testing: Value and Risk

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Annu. Rev. Med. 2021. 72:151–66

First published as a Review in Advance on July 31, 2020

The *Annual Review of Medicine* is online at med.annualreviews.org

https://doi.org/10.1146/annurev-med-070119-114727

Keywords

ethics, genetics, regulation, policy, privacy

Abstract

Although the explosive growth of direct-to-consumer (DTC) genetic testing has moderated, a substantial number of patients are choosing to undergo genetic testing outside the purview of their regular healthcare providers. Further, many industry leaders have been expanding reports to cover many more genes, as well as partnering with employers and others to expand access. This review addresses continuing concerns about DTC genetic testing quality, psychosocial impact, integration with medical practice, effects on the healthcare system, and privacy, as well as emerging concerns about third-party interpretation services and non-health-related uses such as investigative genetic genealogy. It concludes with an examination of two possible futures for DTC genetic testing: merger with traditional modes of healthcare delivery or continuation as a parallel system for patient-driven generation of health-relevant information. Each possibility is associated with distinctive questions related to value and risk.

INTRODUCTION

In early 2019, direct-to-consumer (DTC) genetic testing seemed like an unstoppable juggernaut, with more than 26 million purchases estimated to date and over 100 million purchases anticipated by the start of 2021 (1, 2). Those expectations have moderated. Even before the COVID-19 pandemic brought economic activity to a virtual halt in March 2020, there were reports of slowdowns leading to layoffs at major DTC testing companies such as 23andMe and Ancestry (3). Nonetheless, the number of patients now in possession of genetic test results acquired beyond the purview of their regular healthcare providers is substantial. Further, many industry leaders have been expanding reports to cover many more genes with established or potential health significance and partnering with employers and others to expand access. In sum, physicians and other healthcare providers still have reason to consider the implications of DTC genetic testing, both good and bad, for their patients, their practice, and the healthcare system. A prior review article addressed several ethical, legal, and social issues from the early years of DTC genetic testing, including quality concerns and oversight, the psychosocial impact of testing, integration with medical practice and effects on the healthcare system, and privacy concerns (4). Here, after describing the current state of DTC genetic testing, we update the coverage of those issues. We then describe additional issues that have emerged in recent years, including the intersection of DTC genetic testing with third-party interpretation services. While our emphasis in general is on DTC genetic testing in relation to health, we also discuss several relatively novel non-health-related uses of DTC genetic testing results. In particular, we consider forensic uses and the role results may play in establishing or disrupting views of ancestry and family relationships. Finally, we examine two possible futures for DTC genetic testing. DTC genetic testing may merge with traditional modes of healthcare delivery, or it may continue as a parallel system for patient-driven generation of health-relevant information. Each possibility is associated with distinctive questions related to value and risk.

CURRENT STATE OF DIRECT-TO-CONSUMER GENETIC TESTING

Many of the major DTC testing companies are privately held and do not regularly release sales data. Piecing together information from a variety of sources, one reporter concluded that by early 2019, more than 26 million people worldwide had been tested by the four leading companies, 23andMe, Ancestry, Gene By Gene, and MyHeritage (1). That volume was fueled by aggressive marketing, including discounts in the lead-up to major holidays to promote gifting of test kits. As of May 2020, the undiscounted price of the basic test offered by the leading companies was $59–$99. While all commercial enterprises have natural incentives to attract new customers in order to increase profits, high volume is particularly important for companies like 23andMe with a business model that involves leveraging data to attract research partners in domains including drug development. According to recent company reports, >80% of 23andMe's more than 10 million customers have consented to use of their deidentified data in research, averaging approximately 200 studies per customer (5).

For basic products, reports provide results in domains such as ancestry and traits that are not health-related or only peripherally related, such as a tendency toward dry or wet earwax. In the early years of DTC genetic testing, companies also reported results bearing on health and medical care, including carrier status for cystic fibrosis, likely metabolism profile for drugs like statins, and risk of developing such conditions as cancer, Alzheimer's disease, heart disease, and diabetes. Much of the risk estimation was not well supported by evidence, leading to significant variance in results across companies (4). In 2010, the US Food and Drug Administration (FDA) sent letters indicating its intention to assert jurisdiction over these kinds of tests (6). This occurred against a

backdrop of enforcement discretion for laboratory-developed tests generally. DTC genetic testing was also quite expensive, in the range of $400–$1,000, which limited consumer demand, and most companies besides 23andMe faltered. In 2013, the FDA sent a "cease and desist" letter to 23andMe, effectively halting reporting of health-related results by DTC testing companies (2, 7). However, the ancestry testing market continued to expand, and customers could still access their raw data for independent interpretation.

In 2015, 23andMe again began reporting some health-related information with prior FDA authorization: first carrier status for Bloom syndrome and sickle-cell disease, and then, in 2017, risk information for ten conditions including Alzheimer's disease and Parkinson's disease. 23andMe's addition of results from *BRCA1/2* testing in 2018, again with FDA authorization, generated more controversy, as described below. In 2019, 23andMe added a polygenic risk score for type 2 diabetes to its Ancestry + Health product. (A polygenic risk score uses findings from genome-wide association studies and other data to quantify the effect of variants in many different genes in the aggregate on risk for a complex disease.) 23andMe did not seek FDA authorization, based on its interpretation of FDA guidance for low-risk general wellness products (8). Since polygenic risk scores have the cachet of cutting-edge science, other DTC testing companies appear poised to follow 23andMe's lead in incorporating scores in their health-focused products (9).

Like 23andMe, other established DTC testing companies have recently expanded into the health-related testing space. Several, like Ancestry and Helix, have adopted a variation on the DTC model, known as consumer-driven, physician-mediated DTC, or hybrid genetic testing, that includes a physician order for testing. Generally, the company facilitates testing outside usual care channels by contracting with physicians from a national network to place orders. Ancestry has partnered with PWNHealth, along with Quest Diagnostics and next-generation sequencing developer Illumina, and Helix has partnered with PWNHealth and the Mayo Clinic (10). Some companies adopting this model have developed products utilizing next-generation sequencing rather than chip-based genotyping. For example, Veritas Genetics made a splash in 2016 by offering whole-genome sequencing for under $1,000 (11). The "hybrid" label has been used most often to describe a scenario in which a company focused on traditional clinical or medical-grade testing, such as Invitae, develops a consumer-driven option (12). Color Genomics, for example, has been pursuing partnerships with large organizations to offer free or subsidized genetic testing to employees or customers (13).

Although trend lines once led enthusiasts to anticipate continued exponential growth in DTC genetic testing, recent reports have undercut those expectations, as noted above. The slowdown has been attributed to an absence of enthusiasm beyond a limited pool of early adopters, as well as increasing concerns about privacy due to general erosion of trust in major technology companies and developments such as law enforcement interest in genetic databases. Commentators have suggested that DTC testing companies respond to setbacks by emphasizing newer health-focused offerings (3, 14). The extent of the public appetite for these products, which are still largely not covered by insurance, is unclear.

More general economic setbacks are likely to reinforce the current trend toward retrenchment. At the same time, many Americans, especially white Americans of high socioeconomic status, have embraced DTC genetic testing (15). An interest in genealogy may lead to purchase of a modestly priced health-focused supplemental product. Further, in a time of economic hardship, patients who have a concerning family history and would meet criteria for insurance coverage of clinical genetic testing, but are uninsured, may view DTC genetic testing as an affordable alternative. In both these scenarios, there may be significant implications for personal and familial health and well-being, as well as the health system. A recent National Academies workshop highlighted hopes that DTC genetic testing could be a way to address access-to-care gaps and further research; it

also provided grounds for skepticism (15). Finally, non-health-related uses of data generated by DTC testing companies may affect patient attitudes toward traditional as well as DTC genetic testing. For all these reasons, DTC genetic testing remains worthy of serious attention.

TEST QUALITY AND MARKETING

With the re-entry of DTC testing companies into the health space, quality and marketing concerns are once again prominent. Products that include testing only for highly restricted sets of variants in a few genes or, at the other end of the spectrum, encompass next-generation sequencing-based panels or polygenic risk scores, raise distinctive issues (16). The 23andMe addition of *BRCA* testing is a good case illustration of the former. On March 6, 2018, the FDA authorized 23andMe to expand its DTC genetic test to include selected variants in *BRCA1* and *BRCA2*, two genes linked to breast and other cancers. Specifically, the 23andMe test is designed to detect three pathogenic variants that are most common in people of Ashkenazi Jewish ancestry. These variants are present in approximately 2% of Ashkenazi Jewish women; prevalence drops to 0–0.1% for other ancestry groups. The test was reviewed through the FDA's pathway for novel, low-to-moderate-risk devices. Along with the specific authorization of the 23andMe test, the FDA established special controls setting forth the agency's expectations for accuracy, reproducibility, clinical performance, and labeling. Once a company has obtained authorization for what the FDA considers a "Genetic Health Risk" test (versus a higher-risk "Cancer Predisposition" test), it is permitted to offer most similar tests without additional FDA premarket review (17, 18).

While the value of true population-wide screening for pathogenic variants in *BRCA* genes is unclear, there is evidence that screening some groups, such as Ashkenazi Jews, could be beneficial (19). Women who have learned about a pathogenic *BRCA1/2* variant via a 23andMe test have reported being grateful for the information, even if the result was unexpected (15). However, many of the articles in the popular media and academic journals expressed strong reservations about the test and the FDA's approach to regulation. A common concern has been that individuals receiving a negative result for the three *BRCA* variants will conclude that they have no reason to worry about breast cancer and forego other indicated steps such as routine mammography or consultation to assess indications for clinical genetic testing. As part of the FDA review process, 23andMe submitted educational materials and relied on results from earlier user comprehension studies, which generated an overall comprehension score greater than 90% (20, 21). There is anecdotal evidence that some individuals may understand the limits of 23andMe testing as an intellectual matter and yet still derive false reassurance. For example, NPR (National Public Radio) profiled three women who seemed to grasp the limitations and verbalized that they could not rely on results; still, after receiving a negative result, a woman who had a family history of breast cancer and no health insurance told the reporter, "Now I feel a little bit better about waiting [to see a doctor for a mammogram or clinical testing]. Beforehand, I probably would have not waited and figure[d] out a way to afford this" (22).

More directly related to test performance, concerns have been expressed about false positives. In the case of the *BRCA* test, the FDA concluded that 23andMe had provided sufficient data to establish test accuracy (i.e., correct identification of the three genetic variants in saliva samples) and reproducibility of results. In addition, an analysis by investigators from Ambry Genetics confirmed pathogenic Ashkenazi Jewish founder variants in *BRCA1/2* consistent with initial findings based on DTC genetic testing by a range of companies. At the same time, Ambry did not confirm positive findings for eight other *BRCA1/2* variants, and there were significant false positives for variants in other genes (23). However, it is important to note that the Ambry analysis was inclusive of variants identified in raw data. Hence, the term false positive is potentially misleading, since the

analysis was not limited to positive results in DTC company test reports. Nonetheless, 23andMe itself advises confirming the results it reports in a clinical setting before taking any medical action, consistent with FDA special controls (20).

Some commentators have suggested that the adequacy of consumer education before testing and in the context of results disclosure is a particular concern for panel testing (24). Panel testing involves multiple genes (typically 25 and up) with varying degrees of penetrance and clinical relevance. It has greater potential to produce uncertain results, such as identifying variants of uncertain significance or wide risk estimates. Polygenic risk scores are considered promising but with utility yet to be fully established (25). To the extent that each company generates its own algorithms, reporting of scores may mark a return to a feature of the first era of health-related DTC genetic testing: substantial variation in risk estimates across companies. Also, the potential benefit of scores for non-European subpopulations is unclear, since the research databases that are the foundation for development are heavily skewed toward European ancestry (15). Finally, in the case of type 2 diabetes, some commentators have pointed to the significant impact of weight and suggested that a bathroom scale would be about three times as effective as the 23andMe test in identifying those at risk (8). 23andMe's accompanying educational materials do allow customers to further refine their understanding of risk by selecting from a drop-down menu that includes other factors. As noted above, the FDA has issued guidance for general wellness products it will not scrutinize. To qualify, products must (*a*) be intended only for general wellness use (which includes connecting "the role of healthy lifestyle with helping to reduce the risk or impact of certain chronic diseases or conditions. . .where it is well understood and accepted that healthy lifestyle choices may play an important role in health outcomes for the disease or condition"), and (*b*) present a low safety risk to users or others (18).

In addition to the FDA, other regulators of test quality and marketing include the Centers for Medicare and Medicaid Services (CMS), the Federal Trade Commission (FTC), state agencies with oversight of testing, and professional societies. CMS is responsible for implementation of the Clinical Laboratory Improvement Amendments (CLIA), focused on the analytical validity of diagnostic tests and laboratory processes. The major DTC firms, including 23andMe, Ancestry, and MyHeritage, conduct testing in CLIA-certified laboratories. The FTC has jurisdiction over commercial enterprises, and it is charged with policing deceptive and unfair trade practices. It holds companies accountable for truth in advertising and conforming their practices to public statements and policies. To date, FTC involvement with the DTC genetic testing industry has focused on privacy, discussed below, and ensuring that companies have evidence to back up health claims. At the state level, the scope of relevant regulation is highly variable, as are agency expertise and resources (26). Many professional societies have modified their statements on DTC genetic testing over time. While concerns persist, some have moved from resistance to tolerance. For example, while the Association for Molecular Pathology initially opposed DTC genetic testing, a recent statement offers cautious support (27).

To the extent that customers of DTC testing companies have opinions about regulation, the evidence suggests that they favor a light touch. This is perhaps unsurprising, given their choice to purchase, but the opinions seem not to be altered by their actual experience with testing. The Impact of Personal Genomics (PGen) Study recruited participants from the pool of customers of 23andMe and Pathway Genomics purchasing products including health-related testing between March and July 2012 (prior to the FDA's warning to 23andMe). Of the total of 1,042 participants completing a baseline survey upon receipt of results and a 6-month follow-up survey, 941 had results that were usable in an analysis of attitudes about oversight. Over 80% were white, were insured, had household income in excess of $40,000, and rated their health good to excellent. At 6 months, 89.9% endorsed a right to access genetic information without going through a medical

professional, and 68.3% supported wider availability. In general, attitudes were unrelated to the nature of the results customers received, but those who reported that they had received many high-risk results did express lower support for wider availability (28). An earlier survey of customers of three DTC testing companies with a similar demographic profile found majority support for monitoring of DTC testing company claims to ensure consistency with scientific evidence but opposition to regulation that would limit access (29).

PSYCHOSOCIAL IMPACT

Psychosocial impact is potentially a very broad category. False reassurance was addressed above, and effects on medical practice, system utilization, and family relationships will be discussed below. This section focuses on three areas of potential impact: perceived benefit/harm and regret (as reported on post-test surveys), anxiety and distress (most rigorously captured through comparisons of pre- and post-test assessments), and changes triggered in mindset. Worries that DTC genetic testing will be a source of widespread psychosocial harm have not been borne out by the available evidence. Most people report appreciation and quickly return to their baseline levels of psychological and social well-being. One might conclude that concerns about psychosocial impact have been put to rest, but given the complete body of evidence, that seems like a mistake. Specifically, there is evidence that individuals vary considerably in their vulnerability to negative psychosocial outcomes and also that certain kinds of results have worrisome effects on mindset.

The authors of a systematic review published in 2015 concluded that evidence of psychosocial benefit or harm from DTC genetic testing had yet to emerge (30). Majorities of the PGen participants reported that testing made them feel more in control of their health (65.8%) and provided them with new knowledge to improve their health (61%). While 38% said they did not consider the possibility of receiving unwanted information, only 2% reported regretting testing and even fewer (1%) reported harm (unspecified) from results (31). An earlier study of purchasers of DTC genome-wide profiling found no significant difference between pre- and post-testing assessments of anxiety symptoms (32). Further, 6.4% of participants experienced a distress response. An analysis of that group did not yield a clear set of meaningful predictors (33). In the PGen Study, consumers who reported poor to fair health were more likely to report disappointment that their test results did not tell them more (31). Finally, even individuals who reported adjusting well to identification of a pathogenic *BRCA1/2* variant through DTC genetic testing expressed a desire for more emotional support at the time of result disclosure (15).

The authors of a more recent overview of psychosocial impacts of all types of genetic testing concluded that "large negative impacts have not been found in the vast majority of people studied" (34, p. S2). At the same time, they noted that mental health is a particularly challenging area, as information about genetic risk can both attenuate tendencies to blame those affected for their problems and promote "prognostic pessimism" (34, p. S7). They also pointed to new evidence suggesting that genetic risk information can become a self-fulfilling prophecy. In a study involving *simulated* genetic testing, Lebowitz and colleagues (35, 36) delivered what they termed genetic feedback at random to participants selected because they were exhibiting symptoms of at least mild depression. Simply being told that their genes predisposed them to depression rendered study participants less confident in their ability to cope. A short educational video emphasizing the nondeterministic role of genes in depression fully mitigated this effect (36). In another study, subjects randomized to the group informed of a genetic predisposition to depression reported significantly more depressive symptoms than those in the group told they were not genetically predisposed, and watching the educational video did not mitigate the effect. Telling people about

a genetic predisposition to hypertension did not have this effect, suggesting that it was not simply a response to negative news (35).

Concerning changes in mindset and the possible physical implications of these changes, Turnwald and colleagues (37) genotyped individuals for actual genetic risk for obesity and then randomized them to receive either a "high-risk" or "protected" result before engaging in a task for which genetic risk was relevant. They found that simply receiving genetic risk information changed cardiorespiratory physiology and perceived exertion and running endurance during exercise, as well as satiety physiology and perceived fullness after food consumption, in a direction consistent with the random risk result. They concluded: "Clinicians, genetic counsellors and direct-to-consumer testing organizations should thus be mindful that the mere act of delivering genetic information can influence actual risk" (37, p. 54).

INTEGRATION WITH MEDICAL PRACTICE

DTC testing has been touted as an important innovation that increases patient autonomy and empowers consumers to direct their own health care. Expanded access to health-related information through DTC testing provides an opportunity for greater partnership between patients and their physicians. For example, patients who receive DTC test results may be better prepared to engage in shared decision making with their physicians and may be more invested in making recommended health and lifestyle modifications (38).

Companies that offer testing are typically clear in expressing that their services are for informational and educational purposes only, and they advise consumers to consult a healthcare professional before acting upon the genetic information they receive (5). Consumers believe that they have a right to access genomic information without involving their physicians but also that physicians should be available and able to provide counseling even though they did not order the tests (15). Yet, this can place a considerable strain on physicians, who (*a*) might be unprepared to counsel patients about test results due to a lack of training in genetic medicine, (*b*) might feel uncomfortable interpreting results and providing recommendations for tests they did not order and cannot assure the validity of, or (*c*) might not have the time to engage in lengthy discussions about test results that may have limited or uncertain health implications for their patients. In a randomized trial of clinical genomic sequencing, physicians reported concerns about their lack of general genetic knowledge and did not feel prepared to counsel patients about genomic test results (39). Yet, in that same study, after a short education session and with access to genetic experts to answer questions, most primary care physicians were able to appropriately communicate and manage the test results (40). When those test results are generated and delivered DTC, the physician may have an added responsibility to clarify the information received and to know when confirmatory testing is indicated (41). Clinical decision support tools may help address some of these concerns but will likely require integrating DTC test results into the electronic medical record, which raises its own set of issues and privacy concerns (15).

Despite the recommendation that consumers consult a healthcare professional before acting on DTC genetic information, not all consumers share their results with their healthcare providers. Among 1,026 respondents in the PGen Study, only 27% reported having shared their test results with a primary care provider, and 8% reported having shared their results with another healthcare provider within 6 months of receiving the results, although 63% reported that they planned to share their results with a primary care provider sometime in the future (42). Among those who did discuss their results with their primary care provider, 35% were very satisfied with the encounter, while 18% were not at all satisfied. Of those who did not share results with a healthcare

provider, 40% reported that they did not think the results were important enough to share, and 37% reported that they did not have the time to do so (42).

Some companies provide access to a genetic counselor (GC) via telemedicine or help their customers identify a GC in their local area if they want. After testing at either 23andMe or Pathway Genomics, only 4% of the 1,026 participants in the PGen Study reported scheduling or planning to schedule an appointment with a GC, although 38% said they would have visited with a GC in person if one had been available to them. Those who pursued testing for health reasons, reported being in fair or poor health, had previously used a GC, or had uncertainty about the results were more likely to seek genetic counseling after testing (43). Although involvement of a GC is generally recommended and the number of GCs in the United States has substantially increased in the past 5 years, the genetic counseling workforce is still small and cannot possibly serve the needs of all customers receiving DTC genetic testing.

Special considerations relate to physician-mediated DTC genetic testing. Often, a physician is responsible for ordering the test on behalf of a consumer, but this arguably creates a physician-patient relationship that gives rise to certain fiduciary responsibilities, including the responsibility to ensure that testing is indicated, that the patient makes an informed decision about testing, and that the results of the test are understood and appreciated. Physicians should not blindly order tests for consumers they have not sufficiently interacted with and with whom they have not established clear expectations, as doing so in the DTC context undermines trust in the profession of medicine more broadly and could expose ordering physicians to potential legal liability.

HEALTH SYSTEMS IMPLICATIONS

DTC genetic testing could have further implications for health systems in at least two ways. First, testing could serve as a catalyst for lifestyle changes that yield improvements in population health, or fill in gaps in access to evidence-based genetic screening and cascade testing. Second, testing could serve as a catalyst for excessive vigilance and heightened demand for interventions unsupported by evidence.

Although many consumers of DTC genetic testing express an intention to modify their lifestyle to address risk factors, studies typically show no changes at follow-up (15, 30). In the PGen Study, 59% of participants said that test results would influence their management of their health (31). However, an analysis of the 762 participants who had complete cancer-related data found that those who received elevated risk estimates were not significantly more likely to change lifestyle or engage in cancer screening than those who received average or below-average risk estimates (44). It may be relevant that no participants tested positive for pathogenic variants in highly penetrant cancer susceptibility genes. As for population health, the Centers for Disease Control and Prevention identify three conditions—hereditary breast and ovarian cancer syndrome, Lynch syndrome, and familial hypercholesterolemia—that are poorly ascertained despite the potential for early detection and intervention to significantly reduce morbidity and mortality (45). The hope is that DTC genetic testing could improve the situation (15). However, DTC genetic testing as currently carried out is likely to fill gaps in haphazard fashion, given the characteristics of purchasers, the scope of available products, and integration issues. Some companies do provide discounted testing to at-risk family members of the original customer in the case of a positive result for a pathogenic variant in a gene like *BRCA1* or *BRCA2*.

Solid evidence regarding potential overvigilance and inappropriate utilization of health system resources as a result of DTC genetic testing is not yet available. In the PGen Study, 4% of participants reported making or planning to make an appointment with a GC (43). With respect to pharmacogenomic results, 5.6% of participants reported changing a medication or starting a

new medication (46). The PGen Study did not include independent verification of self-reports or assessment of appropriateness, and follow-up ended with the 6-month survey. In a study of the experience of physicians within eight Kaiser Permanente regions over 6 months in 2017–2018, just under half of physicians who received at least one DTC-generated health-risk or pharmacogenomic result reported making at least one referral on the basis of the result (47).

PRIVACY CONCERNS

Privacy continues to be a major concern related to genetic testing generally. In the context of DTC genetic testing, some studies have found that consumers report lacking trust in DTC testing companies to protect their information. Members of certain groups have indicated heightened concern owing to their vulnerability to discrimination (48). However, similar lack of trust or perceptions of vulnerability can exist in the context of clinical testing, and some consumers may seek DTC genetic testing precisely because they want to keep information out of electronic health records (15, 48, 49). Consumers are especially worried that genetic information will reach insurers, employers, law enforcement, or hackers and others seeking to use their data for nefarious purposes, and they support laws against access and use by these parties (15, 29).

DTC testing companies have been criticized for the inaccessibility of their privacy policies and what provisions reveal about underlying commitment (or lack of commitment) to customer privacy. Studies have found that privacy policies are often difficult to understand and have gaps in areas such as retention of samples and information, access by third parties, security and breach notification, and consequences of company sale or bankruptcy (49–51). Further, companies typically reserve the right to change their policies at any time, usually without notice to customers. Thus, the onus is on customers to monitor websites for policy changes and navigate the complex requirements for deletion or withdrawal of their samples and data if they note a change that they find unacceptable. There has also been controversy surrounding collaborations between DTC testing companies and technology and pharmaceutical companies, for example, collaborations between Ancestry and Calico, a spinoff from Google, and between 23andMe and GlaxoSmithKline (48, 49). While neither of the examples involved the outright sale and transfer of customer data to a third party, both transactions drew media attention.

Industry leaders have attempted to respond to concerns—and possibly head off more intrusive government regulation—through development and adoption of common standards. The most notable effort at self-regulation to date was the release of "Privacy Best Practices for Consumer Genetic Testing Services" in 2018 (52). This document was published by the Future of Privacy Forum and supported by 23andMe, Ancestry, Helix, MyHeritage, Habit, African Ancestry, and Living DNA (FamilyTreeDNA was an initial supporter but was removed because its agreement with the FBI was determined to conflict with best practices). It addresses transparency, consent, use, transfer and access, integrity, retention and deletion, accountability, security, and privacy by design. For example, companies are to make privacy policies "prominent, publicly accessible, and easy to read" (52, p. 3). Specific consent is required for using data in any manner inconsistent with the policy terms initially provided, onward transfer of a single individual's data, uses outside the primary purpose of the service and inherent contextual uses, proxy submission of a sample for testing, transfer to third parties for research purposes, and use in internal research absent approval through an ethics review process; furthermore, sharing data with employers, insurance companies, educational institutions, and government agencies is expressly prohibited, except as required by law or with separate express consent. However, deidentified information is excluded from these protections.

At the federal level, use of genetic information by insurers and employers is already restricted by the Genetic Information Nondiscrimination Act (GINA). However, there are gaps in GINA's

protections; for example, life, disability, and long-term care insurers and employers having fewer than 15 employees are not covered by GINA. For this reason, educating individuals about GINA may increase rather than allay privacy concerns (53). The Health Insurance Portability and Accountability Act (HIPAA) constrains the flow of personal health information, including genetic information, to third parties. But it applies only to "covered entities" and their business associates. In order to be a covered entity, a healthcare provider must electronically transmit health information in connection with transactions for which the Department of Health and Human Services has adopted standards, such as insurance billing. There is general agreement that DTC testing companies are not covered entities (15, 48). (Hybrid-model ventures are a likely exception.) The FTC has published guidance advising consumers to consider the privacy implications of DTC genetic testing and compare privacy policies before choosing a product (54). Separate guidance for companies outlines steps such as clearly explaining third-party disclosures (55). A company that maintains a database of genetic or other sensitive information for research purposes can apply to the National Institutes of Health for a Certificate of Confidentiality (15).

At the state level, genetic nondiscrimination or genetic privacy laws may provide more extensive protections than GINA, just as laws that protect personal health information or personal information generally may have wider coverage or more stringent mandates than those created under HIPAA (56). States also have consumer protection agencies similar to the FTC, some of which have taken an interest in DTC genetic testing (49). Notably, California recently passed a privacy law comparable to the European Union's General Data Protection Regulation (57).

THIRD-PARTY INTERPRETATION SERVICES

Today, every major DTC testing company gives customers the option of downloading their raw genetic data, and in recent years, a number of third-party services have emerged that offer to expand interpretations of those data beyond what is returned by DTC testing providers. Informational outputs and products offered by third-party interpretation services are diverse and include DNA-customized diet and fitness reports, links to scientific literature or databases, risk assessments, and carrier status results (58). In a 2016 landscape analysis, researchers found that 16 of 23 third-party interpretation services offered health or wellness information (58). In a separate survey of 1,137 self-identified DTC genetic testing customers, these researchers found that 820 had downloaded their raw data and uploaded them to one or more third-party interpretation services (59). Most reported using multiple services (the median number was three), where some uploaders who originally sought non-health (i.e., ancestry or genealogy) interpretations eventually migrated to other services to obtain health interpretations. In follow-up interviews with these cross-over users, one participant explained that they were not interested in third-party interpretation "for health at all," but when they learned of a specific health-related tool, they thought, "Well for five dollars, you know, we'll see what it says" (59, p. 129).

Empirical data that have thus far been collected suggest that uploaders' experiences with third-party interpretation services have generally been positive. Most participants in the previously mentioned survey were satisfied with the information they had received (88%) and reported that their experiences with the third-party interpretation landscape had increased their understanding of genetics in general (76%) and how DTC testing companies interpret genetic data (67%) (59). Similarly, in a different survey of 321 DTC genetic testing customers who had uploaded their raw data to a third-party interpretation service, 93% reported being satisfied with their decision to do so and 81% were satisfied with the information they received (60). However, these results were inclusive of ancestry and genealogy services and not limited to health services. Further, some uploaders have reported confusion about their results from third-party interpretation services, which

can be exacerbated by misleading color coding of reports (61). Finally, legitimate concerns have been raised about the accuracy of third-party interpretation services' variant interpretations. In the Ambry study, clinical laboratories classified eight variants across five genes as either benign or of unknown significance, whereas those variants were classified by DTC testing firms or third-party genetic interpretation services as "increased risk" (23). The researchers expressed concern that misclassifications can result in unnecessary stress and demands on the medical system, a concern that also has been borne out in case studies involving variants for which there is no consensus on pathogenicity (62).

Although federal agencies have exercised some oversight of DTC testing firms, as described above, they have thus far remained silent with respect to their authority to regulate third-party interpretation services (63). Under CLIA, CMS regulates clinical laboratories, which are defined in a way that seems to require physical engagement with biospecimens. In 2018, the Clinical Laboratory Improvement Advisory Committee (CLIAC), which provides guidance on CLIA standards, authorized a working group to consider CMS's oversight of nontraditional testing models that separate specimen testing from analysis and interpretation functions. Following the working group's report to CLIAC in April 2019, the committee recommended regulations that would clarify the definition of clinical laboratories to encompass facilities engaged in only bioinformatics activities related to the diagnosis, prevention, or treatment of disease or the assessment of human health (64). Another regulatory area of uncertainty concerns whether third-party interpretation services qualify as medical devices subject to FDA regulation, especially if they are not commercially distributed. Although products intended only to maintain or encourage a healthy lifestyle are not regulated medical devices, the FDA has interpreted patient decision support software as falling within its regulatory authority, albeit perhaps not its regulatory interest (63). Especially if the landscape of health-related third-party genetic interpretation services continues to expand, these and other questions about oversight authority are certain to attract more attention from policy makers.

NON-HEALTH-RELATED USES

The majority of people who do DTC genetic testing are as interested in learning about their ancestry as they are in learning about their disease risk and other traits (31). DNA ancestry tracing can help genealogy enthusiasts better understand the origins and migration patterns within their family tree. Yet, ancestry results can vary widely depending on which company is used (65), and some consumers may discover unexpected information about their ancestry that can be upsetting or disruptive to their sense of self. For example, when 62-year-old Sigrid Johnson, who was black and had always had a very strong identity as an African American, did DTC testing, her results showed her to have <3% African ancestry. This caused her to question her own identity and to feel embarrassed and disappointed: "I was afraid people would think I was a fraud. I was so disappointed, and in my heart of hearts, I didn't believe it, because how could I not be black? I'd lived black. I was black" (66).

Many companies also offer a service where they match customers in their database who share DNA, suggesting that they have a genetic relationship. These relative-matching tools can be very useful to individuals with limited information about their family of origin and can help consumers build out their family tree. However, they can also reveal shocking family secrets and have eroded previous norms around anonymous sperm and egg donation and closed adoption (67, 68). With the ability to connect to genetic relatives through DTC testing, some consumers are discovering that someone they thought was a biological relative may not be, while others are finding new genetic relatives whom they never knew existed. Online communities have formed to help those

who were donor-conceived or adopted connect with siblings or half-siblings and to find their biological parents, most of whom were promised anonymity and never expected to be found (69). While some US sperm banks and adoption agencies are trying to maintain traditional privacy norms, there seems to be growing consensus that this is not a viable long-term option.

During the past several years, these relative-matching tools have proven useful for generating investigative leads when a suspect leaves DNA at a crime scene. By uploading a single nucleotide polymorphism (SNP) profile from the suspect's DNA to a DTC database, law enforcement can use the company's relative-matching tool to identify other customers who might be genetically related to the suspect and use that information to build a family tree, ultimately informing their investigation and helping them to home in on a small number of persons of interest. There has been considerable debate about the ethics and legality of this practice (70), which is commonly referred to as investigative genetic genealogy (IGG). There seems to be general public support for IGG, especially when it is used to help solve violent crimes and crimes against children or to identify missing persons (71). Yet, company practice varies. Some companies refuse to provide law enforcement access to their services without a valid warrant (72, 73), while others allow customers to either opt-in or opt-out of law enforcement matching (74, 75). Regardless of the specific practice, transparency is essential to maintain public trust. Several companies have changed their terms of service to include language regarding law enforcement access to their database, and the Future of Privacy Forum's "Privacy Best Practices for Consumer Genetic Testing Services" includes annual public reporting of law enforcement requests (52).

POSSIBLE FUTURES

At the recent National Academies workshop, Dr. Matthew Ferber of the Mayo Clinic predicted a merger of DTC testing and physician-ordered testing as technologies continue to evolve. Other participants spoke of consumers' desire for unified risk assessment and of a push to standardize certain practices across companies performing genetic testing, such as deposit of data in ClinVar, a public archive of reports of variant–phenotype relationships. Indeed, two of the concluding "next steps" from the workshop look like steps down the path toward merger: "developing systems to support providers and patients in the event that DTC testing returns an actionable result" and exploring "incentives for vendors to develop approaches for integrating consumer genomics data into the electronic health record" (15, p. 63). Evolution in this direction could affect value and risk in a number of ways. For example, on the one hand, it should enhance quality and coordination and help to align levels of protection and oversight for all health-related genetic testing. On the other hand, such a merger may entail shifting the healthcare system in a libertarian and consumerist direction, meaning greater deference to the distinctive assessments of value and risk made by individuals rather than professional or expert judgments about matters such as the appropriate indications for and scope of testing. Whether that kind of shift is regarded as risky or problematic will depend on one's general social philosophy.

In an alternative future, DTC genetic testing remains a parallel system. Value would arise from preserving the benefits the FDA recognized in its assessment of 23andMe's newer health-related offerings, such as giving consumers easier access to their own health data unrestricted by geographic location, equipping them to make informed lifestyle adjustments on their own while leaving open the option of partnering with healthcare professionals, and fostering company investment in promoting public awareness of genetic risks. On the risk side of the ledger, this could also mean continuation of differences in protection and oversight based on provider status rather than risk. Further, the limits of generic educational materials and disclaimers and the lack of professional support may continue to create risks of false reassurance and psychosocial harm. It is

unclear whether these risks could be mitigated through mass customization strategies and delivery of support via promising technologies such as chatbots (76). Future research may provide additional insight into the nature of the risk as well as the effectiveness of responses, including studies tracking the behavior of consumers.

DISCLOSURE STATEMENT

C.J.G. is a member of the Investigative Genetic Genealogy Working Group of the Scientific Working Group on DNA Analysis Methods. A.L.M. is a member of the FamilyTreeDNA Citizen's Panel (unpaid position).

ACKNOWLEDGMENTS

We thank Rebecca Hsu and Isabel Canfield for assistance with this project.

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