Direct-to-Consumer Testing 2.0: Emerging Models of Direct-to-Consumer Genetic Testing

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Learning Objectives: On completion of this article, you should be able to (1) evaluate some ethical challenges in the direct consumer access to genetic testing; (2) summarize ongoing changes to the regulation of direct-to-consumer genetic testing in the United States; and (3) predict possible consequences of expanded access to direct-to-consumer genetic testing of clinical practice.

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Abstract

Direct-to-consumer (DTC) genetic testing emerged in the early 2000s as a means of allowing consumers to access information on their genetics without the involvement of a physician. Although early models of DTC were popular with consumers, they were controversial in medical and regulatory circles. In this article, we trace the history of DTC genetic testing, discuss its regulatory implications, and describe the emergence of a new hybrid model we call DTC 2.0.

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A Spit Party is kind of like a Tupperware Party, only the plastic containers are smaller and they're not for leftovers.
23andMe[1]

In December of 2007, an early direct-to-consumer (DTC) genetic testing company celebrated its launch with a Spit Party in which attendees danced, drank, and submitted DNA samples for sequencing. Within weeks, partygoers would have access to a comprehensive report, including their genetic preference for vegetables, whether their tongue curled, and their risk of developing breast cancer. In Silicon Valley, at the height of the dotcom boom, 23andMe was at the vanguard of a wave of interest in personal genomics. Competitors deCODE and Navigenics

also offered genome panels, whereas companies such as Ancestry.com offered to interpret people's DNA and trace their ethnic ancestry.

As the name suggests, DTC genetic testing companies offer genetic tests independent of a physician. Some tests include nonmedical "infotainment" such as ear lobe attachment or the propensity to flush when drinking alcohol. In the past, however, these tests were bundled with risk factors for complex diseases such as type 2 diabetes and osteoporosis or monogenic disease such as *BRCA1* and *BRCA2* for breast and ovarian cancers.[2] Although these genetic analyses had been technically possible for years, the cost of testing was financially prohibitive. In 2007, the cost of a DTC panel hovered around $1000.[3-5] Three years later it dropped to between $300 and $400. By 2012, it dropped to $99 and 23andMe announced their goal of collecting 1 million users.[6]

The users of DTC test products reported that viewing personal genetic risks made them think more carefully about diet and exercise.[7] Online tools allowed users to track the contents of their genome and compare it with that of others. Some products allowed users to conduct a "family search" of the database to determine whether other users may be relatives. "Our DNA is a fascinating aspect of who we are, and we feel strongly that anyone who wants their genetic data should be able to get access to it," the authors of the 23andMe blog posted.[8] Some scientific sources agreed. The journal *Science* named human genetic variation the "breakthrough of the year" and highlighted 23andMe in its coverage. "The best outcomes [of DTC genetics]," wrote the editorial board of *Nature Genetics*, "would be to convert patients into active investigators and navigators of their own health, to make genetics the foundation of medical education [,] and to expand the scope of genetic counseling as a profession."[9]

Fast forward 5 years to 2012, when most DTC companies offering medical information in the United States had gone out of business (although DNA-based ancestry testing remained commercially available). Only one of the early pioneers in this sector remained, and the US Food and Drug Administration (FDA) had temporarily barred it from selling medical information panels. Nevertheless, there was a movement toward a new form of consumer-initiated genetic testing, what we call DTC 2.0.

Fast forward again to 2017, when the FDA has authorized the first DTC test as an approved medical device. Energized by this regulatory development, other companies are actively working to obtain similar approvals. In this article, we review the history of DTC genetic testing products in the United States from an ethical and regulatory perspective. Although the status of these products remains in flux, we will attempt to characterize DTC 2.0 and its potential implications. Direct-to-consumer 2.0 represents a new model of disseminating, using, and interacting with genetic health data, a model that has the potential to be either transformative or disruptive, depending on how key ethical and regulatory challenges are addressed.

RISE AND FALL OF DTC 1.0

The initial rise of the DTC model of genetic testing was, at least partially, a reaction to traditional health care models of providing genetic testing. The medical model is characterized by a dependence on expert knowledge and the structural elements of the health care system. A medical professional, operating within a fiduciary patient-provider relationship, orders clinically indicated genetic testing and licensed, board-certified medical genetic providers interpret and deliver results. The health care system is the mediator of genetic information, responsible for its quality, creation, interpretation, delivery, protection, and implications. In particular, the medical model is committed to protecting the privacy of health information, including genetic information. Patients retain the ability to control which organizations have access to their data. Like all medical care, the model is designed to maximize patient benefit and promote informed clinical decision making while minimizing associated risks.

This medical model has its drawbacks. Private sector actors frequently complain that it innovates too slowly because of regulation and professional resistance to new practices. Some have argued that resistance to new medical decision-making technologies stems from the desire of medical actors to preserve professional autonomy.[10] There is also a lack

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TABLE 1. Key Points of Comparison Between Direct-to-Consumer Genetic Testing and "Traditional" Medical Testing

Key aspect	Direct-to-consumer testing	Traditional medical testing
Testing initiation	Patient initiates test	Health care worker initiates test
Source of regulation	Companies are regulated as consumer products	Health care systems are regulated by industry-specific rules
Information control	Patient controls and manages genetic information	Health care system controls and manages information
Data interpretation source	Patient chooses interpreter of genetic information	Agents of the health care system interpret genetic information
Quality control	Test quality is largely unregulated	Regulations and quality control systems in place to assess test quality
End use	Interpretation can be for multiple purposes, eg, ancestry, paternity, and health	Interpretation facilitates medical management
Pricing model	Intense competition may drive down product price	Product price is tied to the health care payment model
Return of information	Information may come without clinical support or counseling services	Information is delivered by health care professionals
Data interpretation regulation	Information interpreters are typically not accredited	Information interpreters are licensed or accredited
Secondary use	For-profit selling of data for secondary use	Secondary use largely limited to health care research purposes

of skilled medical genetics practitioners; medical genetics is one of the smallest medical subspecialties and many areas of the country are not well served by medical geneticists or genetic counselors.[11] Finally, many see medical genetics as having failed to live up to the hype surrounding human genetics and genomics research. The completion of the Human Genome Project generated enormous public appetite for information on the democratizing promises that spurred unprecedented public investment in genetics. By contrast, medical genetics was focused on restricting genetic information to medical records and expert interpretation.[4]

These drawbacks, combined with the plummeting cost of sequencing and what Wolinsky observes as a cultural motivation toward a "do-it-yourself" American ethic, made the US fertile ground for consumers and suppliers of DTC genetic testing.[12] In contrast to the medical model, the DTC model is premised on a libertarian foundation and disdain for the elitism of expert regulation and control (Table 1). In the DTC model, consumers send a saliva sample by mail and the results are viewed directly via the Internet or a mobile app. Direct-to-consumer proponents regard access to personal genetic information as a "right" that each citizen should enjoy. They cite the convenience of DTC testing, its promotion of preventive and individualized medicine, and reduced costs to both individual consumers and the health care system.[13] Implicit in the promotion of DTC testing is a criticism of the medical profession as being overly cautious about genetic information, with a suggestion that medical professionals are interested largely in preserving their own authority and revenue streams.[10]

Critics of the DTC model countered with their own concerns. Many of the tests on DTC panels were based on genome-wide association studies that found potential associations between single nucleotide point sequence variations and disease outcomes, many of which were not considered clinically robust by medical standards of the time. Furthermore, the information provided by DTC sources was often couched in terms of a percent increase in risk (eg, "40% more likely") without providing additional details about the background risk that served as the basis for the estimate. Medical professionals viewed such language as misleading, especially if the background risk is low (eg, <1%). Without the interpretive help of a health care professional, critics of DTC products maintained that consumers were at risk of misinterpreting genetic test results and making health decisions on inaccurate or incomplete information. Of particular concern was the potential for decreasing health vigilance and the cessation of preventive health behaviors.[5,14] Why should customers exercise or follow a good diet if genetic testing says they are not

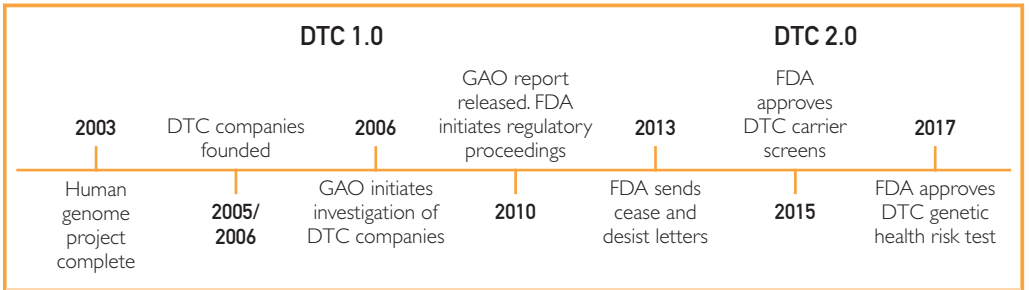

FIGURE. Timeline for DTC 1.0 to 2.0. DTC = direct-to-consumer; DTC 1.0 = direct-to-consumer testing 1.0; DTC 2.0 = direct-to-consumer testing 2.0; FDA = Food and Drug Administration; GAO = US Government Accountability Office.

at risk for cancer? The absence of data on these potential harms made these and other objections to DTC products difficult to counter.

In addition, in making their estimates of background genetic risk, DTC companies were relying on large data sets generated from studies of specific populations. Critics argued that this approach was not sufficiently sensitive to the potential influence of ethnic and racial differences across human populations. Customers who are told they are "negative" for a disease-associated sequence variation validated in 1 population might be given a false sense of security if their genetic ancestry is quite different. Critics also voiced concerns about the potential for unnecessary, expensive, or time-consuming downstream medical testing.

Direct-to-consumer testing emerged within an ambiguous regulatory setting (Figure). Under the Clinical Laboratory Improvement Act (CLIA), which regulates procedural aspects of laboratories that process medical samples, the FDA is tasked with ensuring the safety and efficacy of medical tests and interventions. In addition, the Fair Trade Commission may have regulatory oversight to oversee public claims about regulated products. Historically, the FDA has declined to exercise its right to regulate laboratory-developed tests, an exemption that allowed the rapid development and dissemination of physician-ordered carrier tests for diseases such as cystic fibrosis and Tay-Sachs disease. Although that decision resulted in considerable public health benefits, it also meant that there were no clear regulatory mechanisms in place to assess the analytical validity, clinical validity, and clinical utility of DTC tests.[15]

Although some DTC products included potentially sensitive health information, such as autosomal dominant disease risks, procedures in place to ensure informed consent were poor. These services were framed as a commercial transaction, not as a medical test, making it possible to order a saliva kit and submit a DNA sample without the need to provide the equivalent of "informed consent" to a medical genetic test. Although a user agreement form may have been included as an element of a DTC product, this form often related to future uses of genetic information, not to the testing process itself. Direct-to-consumer critics worried that consumers may not fully understand the health implications of the information they received.[16] Furthermore, buried in these user agreement forms were provisions that allowed DTC companies to retain and use customer data with impunity. This meant that companies could sell aggregate data to third parties or use consumer's data for research without their awareness. These concerns were partially born out when 23andMe filed a patent request in 2012, and several users protested that they had no knowledge that 23andMe intended to profit from their genetic information.

In 2006, the US Government Accountability Office (GAO) launched an investigation into the practices of DTC genetic testing companies.[17] The GAO sent identical DNA samples to 4 companies and compared the results with the help of genetics experts. They also called representatives of each company, posing as a potential customer, to ask about company policies. In their report, published in 2010 and titled "Direct-to-consumer

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genetic tests: misleading test results are further complicated by deceptive marketing and other questionable practices," the GAO wrote that "[our] fictitious consumers received test results that are misleading and of little or no practical use" and found "10 egregious examples of deceptive marketing." The GAO report argued that advertising claims such as "let your DNA help you plan for the important things in life. Take charge of your health and wellness today" overstated the value of DTC test products and their potential to improve personal health.[18]

In response, the FDA sent letters to the 4 largest DTC testing companies on June 10, 2010, informing them that their products constituted medical devices that had not been submitted to the FDA for approval. On July 22 of that year, the House Committee on Commerce and Energy convened a hearing on DTC testing. In his opening statement, Representative Henry A. Waxman stated that government scrutiny was necessary to "ensure the public is protected against exaggerated claims, abusive marketing, and practices that threaten individual health and safety." In November 2013, the FDA went a step further and sent "cease and desist" letters to several DTC genetic testing companies, ordering them to immediately discontinue marketing and sales of their health-related testing services until they received FDA authorization for these devices.[19]

DIRECT-TO-CONSUMER TESTING 2.0

The FDA's shutdown of DTC genetic testing companies was seen as a victory for those who believed this type of testing posed a risk to consumers. More sympathetic commentators argued that the FDA was being overly cautious and stifling innovation.[20] To address the issue, analysts and researchers sought empirical evidence about the effect of DTC testing. A 2011 study conducted by the Scripps Research Institute surveyed individuals before and after accessing a DTC testing product and found "no significant differences in the level of anxiety, dietary fat intake, or exercise behavior between baseline and follow-up for the sample as a whole." A subsequent study in 2013 found that only 24.6% of DTC customers reported any change in levels of anxiety after testing, and 85.3% of those claimed that their anxiety was reduced.[21] Although concerns about the analytical and clinical validity of DTC genetic tests remained, it appeared that objections to DTC testing based on concerns about consumer anxiety or negative changes in health behavior may have been exaggerated. Reflecting this perspective, Timothy Caulfield published an article in *Human Genetics* titled "Direct-to-consumer testing: if consumers are not anxious, why are policymakers?"[21]

Armed with these new data, and motivated by a continuing belief in the potential of personal genomics, industry actors began redefining DTC testing. In 2015, after conducting validation studies, 23andMe received device approval from the FDA for its carrier screen for hereditary Bloom syndrome, making it the first major company to embrace the DTC 2.0 model.[22] As part of its premarket submission, 23andMe conducted not only extensive analytical validation of its test but also extensive user comprehension research. In its approval, the FDA confirmed that the company had submitted evidence establishing that members of the public were capable of correctly interpreting the test report at a 90% comprehension level (although these results were not published in the academic literature).[23]

At the same time, the FDA announced that it would classify DTC genetic carrier screens as lower-risk devices, opening the way to testing for additional autosomal recessive conditions in the future. In doing so, the FDA signaled its willingness to consider at least some forms of DTC medical testing under the regulations. Encouraged, mainstream molecular diagnostic companies began to reenter the DTC space. In 2015, Illumina, one of the largest providers of genomic sequencing in the United States, announced its DTC testing spin-off, Helix. The premise of Helix is a "sequence-once-query-often" model that stores genomic information in a central database and allows business partners to develop DTC testing strategies that interrogate portions of these genomic data sets for its customers.[24]

Color Genomics, which focuses on the BRCA gene test, experimented with a test delivery model in which a physician working for Color Genomics would order genetic testing at the request of a consumer, with genetic counseling provided at no extra charge.[25] Similarly, the carrier screening companies Good Start Genetics and Counsyl

TABLE 2. Key Points of Comparison Between DTC 1.0 and 2.0

DTC 1.0	DTC 2.0
No FDA involvement	FDA exercises regulatory discretion
No medical integration	Increasing medical integration
No analytical validation required	Analytical validation required
No restrictions on panel content	Panel content regulated by risk level
No comprehension validation required	User comprehension validation required
All results integrated	Greater separation between health and entertainment

DTC 1.0 = direct-to-consumer testing 1.0; DTC 2.0 = direct-to-consumer testing 2.0; FDA = Food and Drug Administration.

have their own consumer-facing websites and advertise directly to consumers but work closely with a network of affiliated clinical providers who order their tests. In 2015, Ancestry.com announced that it had begun talks with the FDA about offering a DTC test for disease risk. "We think it's totally appropriate that the FDA has stepped in to pretty aggressively regulate direct-to-consumer genetic tests," said Tim Sullivan, Chief Executive Officer of Ancestry.com, "and we're just starting from that perspective, and trying to work very closely with them."[26]

In April 2017, the FDA announced that after a successful premarket approval process, it had approved the marketing of the first DTC test for genetic health risk (GHR), 23andMe's Personal Genome Service, which tests for 10 diseases or conditions, including Alzheimer risk, Parkinson disease, and hereditary thrombophilia.[27] It also announced that tests for additional conditions would be exempt from premarket review, provided that those tests meet the requirements of the new GHR category. Notably, the FDA declared that the new GHR classification would not apply to diagnostic tests, which they defined as "tests [that] are often used as the sole basis for major treatment decisions."[28] The FDA statement also singled out DTC tests for cancer, prenatal tests, and pharmacogenetic panels, adding that such tests would require separate regulatory review.[28] In issuing this guidance, the FDA signaled a regulatory approach that seeks to allow direct consumer access to some types of health-related genetic information while maintaining stricter regulatory oversight over what it considers to be diagnostic and other more clearly medical results.

These emerging models of DTC genetic testing attempt to strike a balance between the need to ensure consumer safety and the knowledge that personal genomic information is both highly desirable and potentially beneficial to some consumers. Although the exact form and features of DTC 2.0 are still evolving, some important contrasts with DTC 1.0 are clear. The FDA's standards for the quality of scientific evidence as the basis for offering tests and an emphasis on *outcomes* of the tests as key considerations in determining their acceptability are perhaps most characteristic of DTC 2.0. The requirement to exhibit user comprehension signals that DTC 2.0 products will be expected to place greater emphasis on customer education and that genetic information will be considered in the broader context of health, environment, and behaviors. Direct-to-consumer testing 2.0 also calls for greater separation between testing for health information and "infotainment." Although DTC 1.0 companies rejected the protectionist medical model, DTC 2.0 companies will have to embrace a hybrid approach in which modified protectionist strategies are used in partnership with licensed medical professionals (Table 2).

Supporters of this emerging paradigm point to the possibility of identifying presymptomatic diseases in the general population and individuals who might benefit from early medical intervention. In contrast, these early warning signs are useful only if they are founded on robust clinical evaluation platforms, necessitating clinical validation and oversight from both CLIA and the FDA. By virtue of exercising its regulatory privilege, the FDA has announced that the freedom of the individual to access any genetic tests he or she desires has its limits—at least until the test in question reaches minimal quality standards. The FDA's actions suggest that it is considering DTC tests under a broader definition of "medical device" that helps to clarify the pertinent regulatory consideration involved. In addition, all the major DTC 2.0

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actors have taken for granted the necessity to conduct DTC tests in a laboratory that is certified under CLIA so as to ensure safe and accurate laboratory practices. Although the FDA considered 23andMe's premarket application under a de novo status, arguing that the device had no regulatory precedent, the regulatory expectations for other DTC products are clearer after this initial approval. The entire DTC test pipeline—from purchase to online receipt of results—is arguably 1 "device" under the emerging regulatory framework.

The acknowledgment that the product being packaged and sold is medical information, and thus subject to FDA regulation, is perhaps the biggest shift in DTC 2.0 thinking. Diagnostic health information carries its own weight of responsibility, not to mention regulatory restrictions under the Health Information Portability and Accountability Act. Nonetheless, it is not yet clear what ethical or legal responsibilities DTC companies may have to ensure that medical results are not only communicated to customers but are understood and acted on appropriately. It seems clear that the emerging regulatory system will need to develop a hybrid strategy that includes some aspects of the responsibility of medical information providers to ensure the quality of their information, their responsibility to facilitate user comprehension and interpretation of test results, the freedom of consumers to order testing on their own initiative, and the expectation that data will be managed appropriately.

One might speculate on several promising strategies to align the interests of the DTC market and the practice of medicine: improving pretest education to facilitate the kind of informed consent we would expect in a medical setting; separating consent to receive testing by purchasing a product from agreeing to the storage, use, or sale of samples for research; and providing clearer pathways into the medical system in the event of high-risk results by partnering with licensed medical providers to ensure information integrity. It is likely that FDA approval will facilitate the acceptance of DTC 2.0 tests by health insurance payers but a collaborative approach by all stakeholders would facilitate the process considerably. Finally, it will be essential to provide a supportive environment for consumers that acknowledges both the entertaining and potentially worrisome nature of genetic information and provides for counseling and follow-up.

An area of evolving compromise is the relationship between providers, consumers, patients, and medical health information generators. In their representations in the past, DTC testing companies have framed themselves as service providers with no relationship with their consumers beyond a commercial one. Several DTC companies encourage their customers to engage with online social media platforms and respond to follow-up surveys and health reports. This is an entirely voluntary relationship, with no obligations to either side. Even when customer samples are placed in a proprietary database and used for commercial purposes, there is no reciprocal obligation to customers to report on, or share in, the benefits of those programs. It seems clear, however, that one of the most cogent critiques of earlier DTC models was this attempt to flatten this relationship to a purely commercial purchase.

There is, however, precedent for offering information *relevant to health behaviors* in a DTC digital platform. Numerous websites offer screening for obesity using self-reported body mass index statistics, and several websites or software services will allow individuals to construct a pedigree that may indicate a family history of inherited disease. Neither service constitutes diagnostic medical information, and the only existing framework for the discovery, return, and follow-up of diagnostic medical genetic information is the medical model. Thus, it remains to be seen how DTC 2.0 may evolve into a new model of health care interaction.

CONCLUSION

As evidenced by the timeline shown in the Figure, the realm of genetic testing and consumer health is evolving at a lightning pace. The combination of intense commercial competition, high consumer interest, and large-scale research on the effect of genetics on human health has combined to form an intense and rapidly shifting landscape. The evolution from DTC 1.0 to DTC 2.0 is characterized by an end to the clear division between medical and DTC models and the emergence of a hybrid approach that seeks to allocate forms of genetic information to one category or the other. The approach is in its early stages, and it remains unclear how successful

the DTC 2.0 model will be in the marketplace or in public health settings. Nevertheless, it is clear that genetic information is increasingly moving out of medical institutions and into the private commercial sector. If they succeed, DTC 2.0 companies may usher in new collaborations between patients, consumers, medical providers, and regulators that maximize the benefits of genetic information through the empowerment of patients and providers.

Abbreviations and Acronyms: **CLIA** = Clinical Laboratory Improvement Act; **DTC** = direct-to-consumer; **FDA** = US Food and Drug Administration; **GAO** = US Government Accountability Office; **GHR** = genetic health risk

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