ABSTRACT

Analysis of Perceived Benefits and Potential Harms of Direct-to-Consumer Genetic Testing with Regard to Improving Regulation

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Direct-to-Consumer (DTC) genetic testing has been historically under-regulated. Since the development of DTC genetic testing in 2002, regulations have been slowly accumulating with the creation of legislation such as the Genetic Nondiscrimination Act of 2008 and the FDA's 2010 decision to deem DTC genetic tests as medical devices requiring FDA approval and regulation. There are still gaps left by current regulations that must be filled through improving upon current regulations and establishing new legislation. When considering the need for improved regulations, it is important to recognize the reason consumers pursue such testing. Understanding consumer motivations helps to create regulation that avoids impeding benefits received from testing and ensures consumer protection by mitigating potential harm and risks from DTC genetic testing. This thesis provides a history of DTC genetic testing and analyzes consumer motivations, risks, and benefits to be taken into consideration for future regulations.

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# ANALYSIS OF PERCEIVED BENEFITS AND POTENTIAL HARMS OF DIRECT-TO-CONSUMER GENETIC TESTING WITH REGARD TO IMPROVING REGULATION

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# CHAPTER ONE

## History

In 1988 the Human Genome Project started by the U.S. National Academy of Sciences set out to sequence the human genome - a journey requiring international effort. By 2003, this goal was accomplished through the National Institute of Health and the Department of Energy, unlocking the three billion base pair sequence of a human genome (*Human Genome Project Results*, 2018). One year before the completion of the Human Genome Project, in 2002 Myriad Genetics began advertising the first Direct-to-Consumer Personal Genomic Test, BRCAnalysis, testing for BRCA1 and BRCA2 mutations that increase breast and ovarian cancer risk (Brower, 2010). Only five years later, November 16th, 2007, marked the launch of the first DTC genetic testing panel, "deCODEme" by the pioneering genetics company, deCODE, founded in Reykjavik, Iceland (*Decode Launches Decodeme™*, 2007). The US company 23andMe announced their DTC genetic testing service the very next day (Wade, 2007). Meanwhile the reference genome that was completed in 2003 by the Human Genome Project was continuously being updated and added to. The Telomere-to-Telomere Consortium was founded in 2019 to fill in the missing eight percent of the human genome in hg38. On March 31st, 2022 the first complete sequence of the human genome was published by the Telomere-to-Telomere Consortium. The sequence includes "gapless assemblies for all chromosomes except Y, corrects errors in the prior references, and introduces nearly 200 million base pairs of

sequence containing 1956 gene predictions" (Nurk et al., 2022, Abstract). The completed sequencing of the human genome comes twenty years after the first marketed DTC genetic test and fifteen years after deCode launched the first DTC genetic testing service.

In deCODEme's launch statement, CEO Kari Stefansson, MD, PhD is quoted enthusing that, "You have the opportunity to take advantage of the best that science has to offer when you learn about disease risks associated with your genetic variations..." (*Decode Launches Decodeme™*, 2007, para. 6). At the time of launch in 2007, "the best that science has to offer" on disease risks from genetic variations was not promising. While the science of genetic variations had made significant advancements in a fascinating speed before deCODEme's launch, there was still a long way to go before the science could support the company's claims and ambitions. As stated above, the human genome still had a large chunk - 8% - missing until 15 years after the company's launch. In an opening statement to the 111th Congress in 2010, Hon. Michael C. Burgess stated, "No one should be required to make an irreversible health decision, such as a surgical procedure, based on unsettled or evolving science" (Direct-to-consumer genetic testing, 2010, p.10). The science behind DTC genetic tests was still ongoing at the time that DTC genetic testing companies launched. This is shown by the continuous updates and expansions that were made to the human genome sequence. Therefore, health decisions should not have been made on the basis of DTC genetic test results which was encouraged by the DTC genetic testing companies providing health information in their test results.

In addition to the ever-evolving reference genome, the diversity among the data being used for these tests was also severely limited at the time of their release. The 1000

Genome Project was launched in 2008 to expand on the information provided by the human reference genomes. The project sequenced the genomes of 2,504 different consenting individuals with the goal of increasing knowledge of genetic variation in humans. Although the project sequenced genomes from five different major continental regions, a 2019 study by Belsare et al. displayed that the 1000 Genome Project was limited in application to those of European descent. The study was focused on evaluating the 1000 Genome Project and the quality of its data. It was found that since there had not been large-scale sequencing on non-European ethnicities, imputation studies involving less researched populations would have a larger error rate than European studies. This was due to the rareness of region-specific variants in the current reference panels. The study also found that European studies had limited applicability to non-Europeans. The Belsare study is quoted stating,

> In summary, while the 1000GP and HRC provide valuable genomic resources that can augment the power of GWAS in groups with European ancestry, additional large-scale genome sequencing of diverse human populations will be necessary to obtain comparable benefits of imputation in genetic association studies of non-European groups. (Belsare et al., 2019, p.10)

The mission of the 1000 Genome Project to expand knowledge of genetic variation - which was still limited in application to one ethnic population - started a year after the launch of DTC personal genomic testing companies. The project was not completed until eight years after the first DTC genetic testing company, deCODE, launched. A representative for 23andMe, Ashley Gould, admitted in her 2010 testimony to the 111th congress that, “Unfortunately, most of this research, which has been NIH-funded, has primarily been done in European populations” (Direct-to-consumer genetic testing, 2010, p. 172). She also stated in her testimony that 23andMe was hoping to take part in research

to correct this disparity. The International Genome Sample Resource (IGSR) began at the end of the 1000 Genome Project in 2015. IGSR is a resource dedicated to ensuring accessibility of data from the 1000 Genome Project and generating new data from new samples in a similar fashion. One of the three declared goals of the IGSR is to "expand the data collection to include new populations" (The International Genome Sample Resource, n.d., sec 3). This goal comes eight years after the launch of DTC personal genomic testing companies and thirteen years after the first DTC genetic test was marketed.

In the 2010 investigation done by the Government Accountability Office, it was discovered that one company informed customers of African American descent that the limited research in this ethnic group allowed them to only provide four test results for Lupus, Type 2 Diabetes, Alzheimer's, and Prostate Cancer, while those of Caucasian descent were provided a much larger amount of test results (Direct-to-consumer genetic testing, 2010). These limited test results for African Americans were due to the fact that DTC personal genomic tests look only at a handful of the known variants for different genetic diseases, when in reality there are an increasing number of variants that could lead to the genetic diseases. The variants being looked at in DTC genetic tests are the most common to certain populations such as those of European or Ashkenazi Jewish descent. Other ethnicities may have other variants that would be more likely for that population and would therefore be missed by the DTC genetic tests. A 2019 study by the American Society for Human Genetics was done on false negatives reported for colorectal causing variants in the MUTYH gene. It was discovered that "100% of Asians, 75% of African-Americans, 46% of Hispanics, and 33% of Caucasians would have

received clinical false-negatives" (American Society of Human Genetics, 2019, para. 9). This shows that DTC genetic testing may give false hope to those of non-European ethnicities because the false-negative rate is much higher in comparison to Caucasians. When someone receives a false-negative result they may be given false hope by thinking they are free of a disease that they may later develop. This phenomena of disproportionate false-negative rates is explained by the earlier concept of the tests being of limited utility to non-European backgrounds due to the large error rate in imputation studies from a lack of large-scale research done in these non-European ethnicities.

From the launch of the first DTC genetic testing companies in 2007 until 2010, the DTC genetic testing industry continued expanding with the only oversight being over labs conducting the tests by the Centers for Medicare and Medicaid under CLIA, the Clinical Laboratory Improvement Act (Direct-to-consumer genetic testing, 2010). CLIA ensured that the laboratory that was performing the genetic testing was up to federal quality standards but did not regulate how the information from these tests was interpreted or presented to consumers of DTC genetic tests.

The FDA regulates anything deemed as a “medical device” - an item involved in diagnosis, cure, mitigation, treatment, or prevention of disease (U.S. Food and Drug Administration, n.d.). DTC genetic testing companies argued that they did not believe they required FDA approval because their tests were not intended as diagnostic, but were instead risk assessments (Direct-to-consumer genetic testing, 2010). At the same time however, DTC genetic testing company representatives argued that a benefit for public health from DTC genetic testing was that the tests encourage consumers to take preventative measures such as increasing exercise and maintaining a healthier diet to

decrease their risks. In that case, DTC genetic testing could have then fallen under FDA authority as a medical device due to the preventative aspect.

DTC genetic testing companies that began in 2007 had less ambitious claims focused on ancestry and physical traits with less than 20 medical claims. Despite the fact that there were still medical claims being made, the FDA did not require their approval as they did not consider the tests to be a medical device. Over the years these claims grew immensely. One company started out with 17 health claims in 2008 and grew to 100 health claims by 2010 (Direct-to-consumer genetic testing, 2010). The FDA began to take action in 2010 when they received the news that Pathway Genomics' DTC tests would become available in over 6,000 Walgreens stores and 23andMe would begin marketing through Amazon's website. At this point the FDA sent letters to five DTC genetic testing companies informing them that they were considered to be selling medical devices and must receive FDA approval before continuing to market their products. The FDA also sent a letter to Illumina Inc., a popular genetics laboratory, for providing these companies with genetic tests (Direct-to-consumer genetic testing, 2010).

From the timing and motivations of the FDA's cease and desist letters, it seems as though the FDA condoned unregulated selling from these DTC genetic testing companies in early development mainly because they reached a smaller market. When the companies began receiving popularity and casting a wider net in their marketing, they were blindsided by FDA regulations. The companies had tested the waters with a minimal number of health-related tests and when those went without repercussion, they felt comfortable to expand at a rapid pace without supervision.

# CHAPTER TWO

## Consumer Motivations

The rapid expansion of DTC genetic testing companies would not have occurred without an increasing consumer interest in DTC genetic tests. The motivations behind why consumers purchase these tests provides insights into how they are being used, how they should be produced and what regulation should be in place. Many of the companies that offer DTC genetic testing offer a variety of services from health information to ancestry information and traits. While ancestry and traits can be categorized as more for entertainment reasons, health information received from these tests is what led to FDA regulation as it relays more sensitive personal health information. If consumers are more motivated by curiosity and entertainment such as ancestry and traits, then it may not be necessary for the production of health-informative DTC genetic testing to continue. Companies could instead switch their focus onto DTC genetic testing for ancestry, traits or other tests for entertainment purposes as there is a higher demand for these types of tests. If consumers are motivated to pursue health-informative DTC genetic testing, then it is shown that such tests have a higher demand and the FDA needs to provide greater regulation of these tests to ensure the consumer is given accurate and beneficial information from them. Some DTC genetic testing companies, such as OME Care, formerly known as Pathway Genetics, offer only health-informative tests (OMECare, 2021). Understanding the motivations behind why consumers pursue health-informative DTC genetic tests provides insights into the way in which they should be regulated.

Whether the patient is motivated by seeking a diagnosis, a desire to understand risks, wanting to plan for the future, or seeking motivation for lifestyle changes; what the consumer hopes to get out of these tests can influence the way in which they need to be regulated so that the consumer expectations may be fulfilled in an accurate and beneficial way.

Two studies over the motivations for consumers pursuing genetic testing were looked at. One study was done previous to the 2013 FDA intervention and one study was done more recently in 2017. For both of these studies the results were not mutually exclusive meaning participants were able to choose multiple areas of interest. A study by Roberts et al. was conducted in 2013 before the FDA involvement in DTC genetic testing and the study was later published in 2017. This 2013 study listed consumer motivations for pursuing DTC genetic testing as 74% interest in ancestry and a tie of 72% interest each for trait information and disease risk (Roberts et al., 2017, pp.36-45). The results of a 2019 study by Nelson et al. after the involvement of the FDA, listed general curiosity as 68% of participants claiming it as a very important motivation, ancestry as 66%, finding relatives as 46.9%, disease risk as 31.4%, having a limited family health history as 20.7%, other family members pursuing testing as 10.7%, participating in research as 32.3%, and wanting their raw genetic data as the main consumer motivations in pursuing DTC genetic testing (Nelson et al., 2019, pp.122-131).

In comparing the two studies, an interest in disease risk has significantly lowered from 72% interest before FDA involvement to only a 31.4% interest after. Possible explanations for this decrease in interest could include a lack of trust from consumers in the accuracy of disease risk genetic tests now that websites have included more

educational information on the limitations and accuracy of their tests or a lack of interest due to the limited number of tests available now that the tests must be FDA approved. In both studies, interest in disease risks was not the top motivation for consumers pursuing DTC genetic testing and in the more recent study, it was not even in the top four motivations. If consumers are less interested in disease risk, it may not be necessary for companies to offer such health focused DTC genetic tests. If the DTC genetic testing companies ceased to offer the tests that provide health information, the tests would no longer be classified as a medical device and would not need FDA regulation.

There are DTC genetic testing companies that offer only health-informative genetic tests, displaying that there must still be a significant market in the health-informative DTC genetic tests. A 2021 study by Pavarini et al., for example, studied the motivations of young adults with a family history of Alzheimer's to either pursue or not pursue DTC genetic testing for Late-Onset Alzheimer's (Pavarini et al., 2021). This study was conducted after FDA involvement in DTC genetic testing as the article was published in June 2021. The study found the main reasons for pursuing DTC genetic testing for Late-Onset Alzheimer's disease in young adults with a family history were "self-knowledge", "life planning", "reprioritizing values", "aiding research", and "prevention" (Pavarini et al., 2021, fig. 3). The young adults that believed this testing should be available to them stated a "right to knowledge and access" and a "right to non-interference" as their reasoning (Pavarini et al., 2021, fig. 2).

The FDA approved DTC genetic test for late-onset Alzheimer's looks for the ε4 variant of the three major allelic variants in the APOE gene. According to the article mentioned above, "Variations in the APOE gene are, however, only one among many

factors that influence a person's risk, and the presence of APOE ε4 is neither necessary nor sufficient for developing the condition" (Pavarini et al., 2021, p.1). The motivations previously mentioned behind pursuing this testing, do not conflict with the idea that the test has limited clinical utility. The category of "prevention" as a motivating factor for testing means the consumer is seeking the test in order to motivate them to engage in preventative measures if they are shown to be at a high risk. This motivator of "prevention" is the only category that implies the consumer will be actively altering their health based on DTC genetic testing. The current preventative strategies for Alzheimer's disease as recommended by the Alzheimer's Association are increasing exercise, following a heart healthy diet, maintaining social connections and mental stimulation, and receiving flu and pneumonia vaccinations (Alzheimer's Association, n.d.). All these preventative measures are recommended for increased health in general and will not be harmful if the consumer engages in them no matter their Alzheimer's risk. The motivations of "life planning" and "reprioritizing values" also can be meaningful activities regardless of Alzheimer's risk and do not pose a threat to the consumer's well-being.

According to the earlier mentioned study by Pavarini et al., the main motivation for the pursuit of DTC genetic testing for late-onset Alzheimer's disease is "self-knowledge" or wanting to know oneself better. This is a more potentially harmful motivation as it could lead to psychological distress. Although study participants believe they have a right to know their disease risk, it would potentially harm their well-being rather than improve it. As Alzheimer's disease is a progressive disease with no current cure and the only preventative measures are partaking in a healthier lifestyle, knowing

one's risk of Alzheimer's has little benefit to one's health. However, knowing one has an increased risk for late-onset Alzheimer's disease could cause unnecessary stress about the possibility of developing a disease that is not guaranteed to develop. On the other hand, knowing one is not at an increased risk may lead them to have false confidence and could be psychologically damaging if they unexpectedly develop the disease later in life. Emphasizing the lack of clinical utility and predictiveness of the test may decrease the potential psychological harm from discordant results, making the test worthwhile for satisfying the consumers expectations and motivations.

A 2021 study by Peck et al. conducted on the motivations of DTC genetic testing consumers seeking out polygenic risk scores can provide insight into the motivations of consumers pursuing health-informative DTC genetic tests. Polygenic risk scores summarize the results of a multitude of variants that play into effects of a single, genetically complex disease and provide an overview of the risk of developing or having that disease based on genetic variants. DTC health-informative genetic testing is often a precursor to seeking out polygenic risk scores through the raw data given by DTC genetic testing companies. In some cases, DTC health-informative genetic testing provides polygenic risk scores as the testing result. Therefore, motivations behind those seeking polygenic risk scores from their genetic data can be easily applied as motivations behind those seeking the similar results of DTC health-informative genetic testing. The study by Peck et al. depicts the main reason for seeking polygenic risk scores as 80% being generally curious, slightly over 50% as access to health information, approximately 25% to guide lifestyle changes, slightly less than 25% for ancestry, approximately 15% for children/grandchildren, approximately 13% for family history, approximately 11%

wanting a diagnosis, approximately 8% to determine guaranteed conditions, and approximately 7% for family planning (Peck et al., 2021).

The main motivation for seeking DTC health-informative genetic testing as being "generally curious" is a promising argument both for and against the selling of these tests. As an argument for DTC health-informative genetic tests, the motivation of curiosity places little expectation from the consumer over the usefulness of the test. Although a somewhat vague motivation, it would seem "curiosity" does not imply that life changing decisions will be based on DTC genetic tests or that the consumer is hoping the test will provide a drastic revelation for their health. The motivation of simple curiosity pushes these health-informative tests closer into the category of tests with entertainment purposes.

The downside of general curiosity as a major motivator in DTC health-informative genetic testing is that if the consumer's main goal in pursuing these tests is to satisfy curiosity with possible entertainment value, the consumer may not be properly mentally prepared to receive the knowledge that comes with the test result. When sought for curiosity's sake, the testing may put an unnecessary psychological burden on the patient/consumer to find out they might or might not develop a devastating, untreatable condition or to be told they are at a "low risk" for a condition they already have. When health-informative tests are sought for the motivation of curiosity, it leaves open space for confusion and misunderstanding of test results and their usability. "Curiosity" being the main motivation to pursue health-informative DTC genetic testing can be used as an argument against DTC health-informative genetic testing as it might not be worth satisfying consumer curiosity at the risk of damaging consumer well-being.

# CHAPTER THREE

## Perceived Benefits

Consumers are motivated to participate in DTC genetic testing due to the various perceived benefits. The benefits to consumers stem from the convenience of not having to go through health providers or health insurance which may block access to genetic tests due to protocols and cost. A 2013 study by Roberts and Ostergren analyzing the benefits, harms, and limitations of DTC genetic testing noted,

> Many proponents of consumer genomics—including direct-to-consumer genetic testing (DTC-GT) marketed publicly to individuals and made available without need for an intermediary medical professional—view direct access to one's genome as an individual right, noting many potential benefits of learning more about one's predilection to disease and likelihood of response to particular medications. (Roberts & Ostergren, 2013, p.1)

Consumers believe they benefit from being able to take their health into their own hands and decide which tests to do for themselves. These perceived benefits include a sense of greater privacy for the consumer, greater motivation to pursue a healthier lifestyle, better health outcomes through early detection and intervention, and lower cost. Better health outcomes and lower cost may hold substantial benefits to the consumers and public health in general. The perceived increase of privacy and motivation to pursue healthier choices, however, may be misguided as DTC genetic testing might not provide these benefits as consumers believe it to. The contradicting risks and harms for each of these benefits will be discussed in the next chapter on potential risks and harms.

### *Privacy*

According to Roberts and Ostergren, many believe that individuals have a right to be able to access their genomic information directly. DTC genetic testing does not require a second person, or "intermediary" to relay the health information to the consumer (Roberts & Ostergren, 2013, p.1). This gives the consumer a sense of security that they are the only one who knows their test results. The consumer does not need to express the desire to pursue genetic testing to another person, nor have the results read by another person. DTC genetic testing allows the consumer a sense of privacy and control over their health information by not having to go through a provider and have results relayed to them. In the case of DTC genetic testing the patient has the knowledge of their health before anyone else does. This claim will be refuted in chapter four on potential risks and harms.

### *Personal Health*

In addition to the perceived privacy, there are benefits to the consumer's personal health that occur with DTC genetic testing. The consumer may benefit from finding a greater sense of motivation to pursue a healthy lifestyle after receiving results of an increased risk for a disease that has preventable measures. The consumer may also benefit from better health outcomes with early detection and screening. Finally, the consumer may be able to pursue testing in pharmacogenetics which allows for a more personalized treatment plan and prevents dangerous adverse effects from medication.

*Motivation for a Healthy Lifestyle*

A popular claim of DTC genetic testing benefits is that results encourage consumers to participate in healthier habits and lifestyles. It is believed that if a consumer discovers that they are at an increased risk for a disease related to obesity, lack of exercise, smoking, etc.; then the consumer will be motivated to take the initiative to get rid of those unhealthy habits and replace them with healthy habits. Perhaps the consumer needs this push to get in the habit of healthy behaviors and finds the genetic test results to be their wakeup call. A 2012 study by Kaufman et al. surveying DTC genetic testing consumers found "sixteen percent of respondents had changed a medication or supplement regimen, and one-third said they were being more careful about their diet" (Kaufman et al., 2012, p.413). This observation was noted by the authors to be associated with how consumers perceive risk based on numerical results. Additionally, the study found that those with a chronic illness or a family history of an illness were more likely to change their prescription medication or start new medications based on DTC genetic test results. Those with a family history were more likely to pay greater attention to improving their diet and those with "poorer self-perceived health" were more likely to make changes in their dietary supplements (Kaufman et al., 2012, p.417). A final important confounding variable discovered in the study is that those who saw a healthcare provider in regards to their DTC genetic tests results were significantly more likely to change a prescription or supplement regimen and pay better attention to improving their diet. This is an important variable as it implies that in order to receive the benefit of motivation to pursue healthier habits, you must forgo the previously stated benefit of a sense of privacy by sharing results with your healthcare provider.

*Early Detection and Intervention*

Early detection and the possibility for early intervention of genetic disease is another benefit to consumers of DTC genetic testing. Early detection and intervention provides consumers with potentially superior health outcomes. A 2013 study by Francke et al. focused on the reactions of DTC genetic testing consumers after receiving BRCA (a gene linked to breast cancer) results. The study stated,

> There were 11 mutation-positive women who received this information through 23andMe for the first time. Among these 11 women the following actions were taken or are planned: one prophylactic mastectomy, three planned mastectomies, three oophorectomies, and four planned oophorectomies (after childbearing). Five said they went to have breast exams and breast imaging after getting their results, and the seven who neither had nor were planning to have mastectomies reported that they would continue to have regular breast cancer monitoring. (Francke et al., 2013, p.12)

Because these women had undergone DTC genetic testing, they were able to use their knowledge of their increased risk of breast cancer and/or ovarian cancer to undergo early intervention procedures for breast and/or ovarian cancer such as mastectomies and oophorectomies. Unless these women had knowledge of a previous family history of breast cancer, the cancer risk may not have been detected early and the women might not have been inclined to pursue these interventions if it weren't for their DTC genetic testing results. Their physicians may not have deemed the interventions necessary without the DTC genetic testing results as well.

A similar benefit of DTC genetic testing is increased screening leading to early detection. The previous 2013 study by Francke et al. showed that women made screening appointments or planned to continue their screening with added diligence after a positive result (Francke et al., 2013). This screening allows for the ability to detect breast cancer in earlier stages. Detecting breast cancer in earlier stages allows treatment such as

chemotherapy and radiation to begin sooner and possibly allows for use of a less severe treatment such as a lumpectomy rather than a mastectomy. Early detection is huge for the consumer's health outcome as stage one breast cancer has a five year survival rate between 98-100% while stage three breast cancer decreases the five year survival rate to between 66-98% (Susan G. Komen, 2021). Early intervention through means of prevention can act as a more imprudent reaction to DTC genetic testing results as it is still unknown whether the disease would have developed or not. Early intervention through means of increased screening may allow for early detection of disease leading to the benefit of better health outcomes for consumers.

*Pharmacogenomics*

Pharmacogenomics is a field wherein genetic testing is done to predict a response to certain medications such as adverse effects, and effectiveness as a treatment. This subset of DTC genetic testing is extremely important in understanding why DTC genetic testing must be regulated as the results give direct medical advice by referring specific medications to consumers. While the patient must still be prescribed the medication by a healthcare provider, the patient may be influenced to ask for a specific medication over another. A 2017 study by Lu et al. was done analyzing the DTC pharmacogenomic testing sold by 23andMe. Out of the 12 pharmacogenomic tests provided with 23andMe results, the study states,

> The FDA considers that pharmacogenetic tests for five of the 12 drugs provide actionable results (fluorouracil, peginterferon alpha, phenytoin, pseudocholinesterase deficiency and warfarin); genetic testing is required for one (abacavir); recommended in two (clopidogrel and thiopurine methyltransferase); one provides informative results (proton pump inhibitor) and the remaining three

> tests have no FDA recommendations (acetaldehyde, simvastatin, sulfonylurea). (Lu et al., 2017, pp.3-4)

The study talks of how five of these tests reflect predictions of effectiveness and adverse effects and the other seven provide predictions of drug toxicity and serious adverse effects. One of them detects acetaldehyde toxicity which puts the patient at an increased risk for esophageal squamous cell carcinoma with consumption of alcohol. The study reviews other pharmacogenomic tests available that can detect an increased risk of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis, both life-threatening, excruciating skin conditions. DTC genetic testing provides a greater accessibility for patients to be aware of their status for genetic results that affect medication. When patients have this information, they are able to avoid medications that they are at an increased risk of adverse reactions for and medications which lack effectiveness in accordance to their genetics. This can prevent death from life-threatening reactions for patients and can save the patient and provider time by not prescribing medications that will prove ineffective to that patient.

### *Public Health*

As DTC genetic testing reaches more consumers, it would be expected to have an impact on public health in addition to the benefits of individual consumers. With more people taking an active role in their health, communities as a whole may see an impact. If a greater population is participating in healthier habits, the community might see the effects of this in obesity and mortality rates. The benefits of DTC genetic testing on public health include lowered health care costs and spending, greater awareness of

genetic disease with an increased motivation of the public to participate in a healthy lifestyle, and the furthering of genetic research.

*Healthcare Spending*

Lowered healthcare costs and spending can be demonstrated through the earlier example of DTC pharmacogenomic tests. DTC pharmacogenomic tests allow providers to not waste time and money on prescribing medications that will prove ineffective or harmful to the health of that particular patient. In a 2017 study by Lu et al. that researches pharmacogenetic testing through DTC company, 23andMe, cost-effectiveness is described as accumulating over years as the patient is prescribed more medications to compare with the results. As the article states,

> Pharmacogenetics is a particularly relevant focus for DTC testing since the test has value throughout life, and need be performed only once. This makes implementation of a pre-emptive pharmacogenetic testing panel potentially cost-effective, since the results can be interrogated when any new drug is prescribed. (Lu et al., 2017, p.6)

DTC pharmacogenetic tests can be applied to medications prescribed throughout a patient's lifetime therefore, results can be taken into consideration before any medication is prescribed. This can avoid wasting money to prescribe medications that will be ineffective for the patient, as well as, avoid the medical costs that can be associated with serious adverse reactions to medications that the patient may be genetically predisposed to. From a long-term perspective, DTC pharmacogenetics are cost-effective ways to reduce medical spending on medications that are ineffective or harmful to patients.

Non-pharmacogenetic tests sold by DTC genetic testing companies also carry the public health benefit of lowering healthcare spending. When an increased risk of a

disease is detected through DTC genetic testing, the patient and their healthcare provider may choose to provide additional or increased screening to monitor for disease onset. The previously mentioned 2021 study by Francke et. al. found that out of 11 women who tested positive for a BRCA mutation, five women had gotten breast exams and imaging and seven had planned to continue their regular monitoring after finding out their BRCA status (Francke et al., 2013). Increased screening may seem a costly effect of DTC genetic testing as not every woman with increased screening will develop the disease. On the other hand, the benefit of detecting the disease early in women who do develop the disease is cost-beneficial. Increase of screening could lead to earlier detection of the disease which could lead to a more cost-effective treatment. Early detection would also decrease the amount of visits and tests that would be otherwise necessary to determine a diagnosis. In a 2017 article by the World Health Organization, it is stated that,

> Detecting cancer early also greatly reduces cancer's financial impact: not only is the cost of treatment much less in cancer's early stages, but people can also continue to work and support their families if they can access effective treatment in time. In 2010, the total annual economic cost of cancer through healthcare expenditure and loss of productivity was estimated at US$ 1.16 trillion. (World Health Organization, 2017, para. 9)

DTC genetic testing benefits public health by facilitating early detection of disease through increased screening which leads to decreased treatment cost and healthcare spending.

*Awareness and Motivations*

DTC genetic testing increases public awareness of uncommon genetic disorders and provides motivation for living a healthier lifestyle, benefitting public health. Through the information gained from the results of DTC genetic testing, consumers are better educated on different genetic disorders and are motivated by an attempt to lower their risk of certain disorders through healthier decisions and lifestyles. In a previously mentioned 2017 study by Roberts et al., it is found that 61% of survey respondents had "learned something new to improve [their] health that [they] didn't know before" and 59.4% claimed "the information [they] received has influenced how [they] will manage [their] health in the future" (Roberts et al., 2017, tbl. 4). By searching through the test results for different genetic disorders, DTC genetic testing consumers are exposed to and gain awareness of the many different genetic disorders that they may not have previously known existed or were genetic.

A longitudinal study of DTC genetic testing consumers that focused on changes of diet and exercise was published in 2017 by Nielsen et. al. This study found that, "Thirty percent of participants reported making a change to their diet that was specifically motivated by their PGT results, and 26% reported changing their exercise based on their PGT results" (Nielsen et al., 2017, p.4). A statistically significant increase in the consumption of fruits and vegetables and ten minutes per day of strength and vigorous exercise was found by this study alongside the generally reported changes in diet and exercise (Nielsen et al., 2017). The Office of Disease Prevention and Health Promotion promotes the public health benefits of better nutrition and increased physical activity. They emphasize that, "Good nutrition, physical activity, and a healthy body

weight are essential parts of a person's overall health and well-being" (Office of Disease Prevention and Health Promotion, 2021, para. 1). According to their statement, 1 in 3 adults and 1 in 6 children in the United States suffer from obesity and conditions related to obesity are among the leading causes of death. Engaging in physical activity and good nutritional habits prevent obesity, therefore decreases the risk of developing certain health conditions and helps to control current conditions (Office of Disease Prevention and Health Promotion, 2021). As DTC genetic testing has been shown to motivate consumers to improve their diet and increase their physical activity, DTC genetic testing provides the public health benefit of improving health outcomes through motivating healthier lifestyles in consumers.

*Research*

In the earlier section on consumer motivations, furthering genetic research was proven to be a common consumer motivation for pursuing DTC genetic testing. Participating in genetic research was listed as a main consumer motivation in the 2019 study by Nelson et al. (Nelson et al., 2019) and the 2021 study by Pavarini et al. (Pavarini et al., 2021). A 2016 study by Laestadius et al. was conducted on data practices among DTC genetic testing firms and found that 9 of the 30 companies they looked into mentioned in their privacy policy and/or terms of service an intention to conduct health-related research and 12 companies mentioned an intention to conduct non-health-related or unspecified research from the DTC genetic tests (Laestadius et al., 2016, pp.513-520). Some of these companies ask for additional consent before using the DNA sample collected from DTC genetic testing for their research while others provide

the option to opt out of research if you desire instead of asking for consent (Laestadius et al., 2016, pp.513-520). According to 23andMe's website, they provide the opportunity to participate in research through answering survey questions that link to that consumer's genetic data and by working with pharmaceutical companies to provide access to clinical trials (23andMe). The company boasts of its four grants from the NIH to fund their research and its multitude of research publications that have come from research done through DTC genetic testing (23andMe). As previously, the science behind these genetic tests is ever evolving and the demand for more genetic research is increasing. DTC genetic testing has the public health benefit of providing an avenue through which the companies can obtain massive amounts of data to accelerate genetic research to find new genetic associations to disease and new treatments for genetic disease.

# CHAPTER FOUR

## Potential Risks and Harms

Each of the previously mentioned benefits of DTC genetic testing have potential risks and harms that accompany them. DTC genetic testing poses a risk to privacy and security through the lack of regulations for DTC genetic testing companies and through the sharing of data with third parties. DTC genetic testing may cause physical and emotional harm to the consumer due to frequent inaccurate results and the lack of genetic counseling involved. Finally, DTC genetic testing leads to an overuse of healthcare which increases healthcare spending. Each benefit of genetic counseling goes along with the potential harms and risks that affect consumers and public health.

### *Privacy and Security*

The benefit of perceived privacy and security from DTC genetic testing is a misguided one. Consumers may believe they are viewing their results privately without anyone else seeing the results first and are therefore in control of the sharing of their health. The problem lies in that “anyone else” excludes the genetic testing company and whomever the company chooses to share the information with. This suggests that the consumer's sense of privacy from DTC genetic testing may be a false sense of privacy and security. In fact, one may argue that DTC genetic testing is actually less secure and private than going through a physician for testing.

A report published in 2020 by Consumer Reports states, "Seventy-eight percent of companies had data sharing provisions that provided genetic information to third parties in de-identified or aggregate forms without additional consumer consent" (Consumer Reports, 2020, p.6). DTC genetic testing companies are not required to be HIPAA compliant and therefore genetic information obtained from these companies is not guaranteed privacy (National Research Council (US) et al., 2010). The Genetic Nondiscrimination Act (GINA) prevents employers and insurance companies from discriminating based on genetic information. While GINA protects genetic privacy for a majority, the military and Indian Health Services are excluded from GINA. (Helm et al., 2015, pp.179-86). This permits the military to discriminate for employment and the military's insurance programs to discriminate from coverage based on genetic testing results. In addition to the gap excluding the military, GINA only prohibits discrimination of insurance on the basis of genetic results for health insurance companies. A 2010 workshop summary on DTC genetic testing states,

> Moreover, DTC genetic testing companies encourage customers to discuss test results with their physicians. As soon as such a discussion occurs—particularly if it results in medical advice, treatment or referral to a specialist—it becomes part of a patient's medical record, which can be requested by life, disability, and long-term-care insurers. (National Research Council (US) et al., 2010, p.15)

Insurance companies outside of health insurance such as life insurance and disability insurance are still able to discriminate from genetic information of consumers.

The 2020 report by Consumer Reports emphasizes the lack of regulation for genetic privacy in DTC companies. The report states, "As there are few rules governing the collection, storage, and disposal of genetic data by DTC genetic-testing companies, consumers' genetic privacy and that of their relatives could be vulnerable to a data

breach" (Consumer Reports, 2020, p.7). Results are often shared with the consumer via the internet, making the health information susceptible to cyberhacking. Another area of concern for the security of consumer genetic data, is the sharing of data with third-parties. Many DTC genetic testing companies partner with pharmaceutical companies and research institutions to provide those companies with genetic data. While the companies for the most part require consent of consumers to share this genetic data, this may still pose a security risk. DTC genetic testing companies often provide information on how the company secures consumer genetic data, but when that data is shared the third-party companies may all have differing security protocols in storing the data that the consumer is not aware of. The security of consumer genetic data is less transparent after data is shared with outside companies.

A lack of clear communication between DTC genetic testing companies and consumers over the storage and use of consumer genetic data poses a risk to consumer privacy. In a previously mentioned 2016 study by Laestadius et al. that analyzes the data practices of DTC genetic testing companies, it was found that of 30 companies only 13.3% stated to consumers the specific amount of time that their data would be held on to by the company (Laestadius et al., 2016, pp.513-520). Only 43.3% of the companies explicitly told consumers what would happen to their genetic data if the company ever went bankrupt or was sold. The intention of using consumer data for health- related research was expressed by only one company on their patient-oriented website, while 9 other companies stated this in their Terms of Service or Privacy Policy page. Another company only stated their intention of using consumer data for research on their corporate website without mentioning it on the patient-oriented webpage. Only 66.7% of

the companies that stated their intention to use consumer data for health related purposes required additional consent from the consumer to do so and some of the companies stated that consent could not be revoked after it was given. Lastly, it was found that none of the companies stated how long data would be stored for use in research (Laestadius et al., 2016, pp.513-520). There is a risk of consumer privacy as companies fail to gain proper informed consent of consumers with a vagueness in the explanations of their practices.

The amount of identifiable information that can be obtained through consumer genetic data is another large risk to consumer privacy. In a 2021 article published by the American Medical Association, the board of trustees is quoted saying, "'In terms of privacy, increasingly it has been recognized that genetic data cannot be de-identified,' the board's report says. 'A DNA profile alone may be adequate to identify most individuals even in the absence of other identifying information, including individuals that have not previously participated in genetic testing'" (Henry, 2021, para. 6). A component offered by both AncestryDNA and 23andMe allows consumers to view predicted genetic relationships to other consenting consumers. This poses a risk for the privacy of family members of the individual pursuing DTC genetic testing. Without providing their own DNA to DTC genetic testing companies, individuals may be identified through the matching of DNA with a more distant relative such as an aunt or cousin. This ability to find individuals who have not consented to DTC genetic testing through the genealogy of those in the company's database can also be a threat to the privacy involved in closed adoptions. An adoptee could match their DNA to a relative of the birth parent and trace that lineage back to the birth parent. This has also been used as a tactic in solving criminal cases with DNA evidence (Brown). When one consents to DTC genetic testing,

they are essentially consenting for their whole biological family as the information discovered affects the whole family and the whole family can easily be traced from the one member's DNA. Another risk to privacy arising from the ethical issues of consent comes from the 2010 investigation done by the Government Accountability Office. It was found that "two companies told our fictitious consumer that she could secretly test her fiance's DNA and surprise him with the results. This secret testing is illegal in 33 States" (Direct-to-consumer genetic testing, 2010, p.33). Therefore, the risk of loss of privacy can come from DTC genetic testing without consent.

### *Emotional and Physical Harms*

The benefit of increased health outcomes and motivation for healthier living does not have as large of an outcome as was hoped and DTC genetic testing may have even provided an opposite effect. A 2012 study by Reid et al. which researched healthcare utilization after multiplex genetic testing - genetic testing that gives results on a large panel of possible variants related to multiple different diseases - had a surprising result that "from the pre-test to the post-test period, the percentage of individuals who had a physician visit per quarter declined by 1.8%" (Reid et al., 2012, p.5). The study saw that consumers actually had less healthcare visits after receiving the results of genetic testing. A possible explanation for this result could be that receiving a negative test result gave the consumer a false sense of security in their health to the point of feeling as though they were healthy enough to not need to visit their physician. Confusion can arise from consumers in the understanding that a negative result is not a negative diagnosis, but rather a negative result for that specific risk factor; there may be other factors that put the

patient at high risk that were not tested for. A negative result is not a reassurance that the disease will never develop. This confusion could also lead to greater emotional trauma if the disease does develop unexpectedly despite the negative DTC genetic test result.

The possibility of an inaccurate test result could cause a similar confusion for the consumer. The 2010 investigation by the Government Accountability office recruited donors to send in the same DNA samples to multiple DTC genetic testing services to compare results. The investigation found, "Donor No. 3 was at the same time at below-average, average, and above-average risk for prostate cancer, high blood pressure, and Type 1 diabetes"(Direct-to-consumer genetic testing, 2010, p.33). The investigation also gave the statistic that, "68 percent of the time the donor DNA samples resulted in different risk predictions for the same disease" (Direct-to-consumer genetic testing, 2010, p.10). A 2018 study by Tandy-Connor et al. found that 40% of gene variants reported in raw data from DTC genetic testing companies were false positives. In addition, the study found that eight variants in genes related to breast cancer and connective tissue disease that were classified as increased risk by DTC raw data are actually classified as benign in multiple clinical laboratories and had too high of frequencies among the general population to be considered as disease causing (Tandy-Connor et al., 2018, pp.1515-1521). Based on these results, it is clear that accuracy of DTC genetic testing results is a problem.

The potential inaccuracy of the DTC genetic tests is a health risk as it may motivate consumers to make unnecessary and potentially dangerous changes to their health. While most treatments or prevention strategies that would cause inaccurate results to lead to serious harm are barricaded by the need for consultation with a physician, the

consumer may make potentially harmful changes to something like their diet on their own as a response to these results. The company Rootine is an example of this. Rootine is a DTC genetic testing company where consumers take a genetic test and the company will create personalized multivitamins for them based on their genetic results (Rootine, n.d.). The repercussions of inaccuracy among this testing could lead to significant and potentially dangerous nutritional imbalances. When it comes to healthcare, serious decisions should not be influenced by tests with results as inconsistent as the Government Accountability Office found DTC genetic tests to be. Dr. Jeffery Shuren summarizes this concern during the congressional hearing of the Government Accountability Office's investigation. He states, "Failure to validate the accuracy, reliability, and clinical implications of the test can result in patient harm from misdiagnosis, failure to treat, delay or inappropriate treatment, or avoidable adverse events. Those risks can be increased when the test is marketed directly to consumers without medical advice or genetic counseling" (Direct-to-consumer genetic testing, 2010, p.68).

Inaccurate results can also lead to increased emotional trauma in addition to physical harm. A quote from the congressional hearing on the Government Accountability Office investigation says, "This pacemaker controlled this donor's atrial fibrillation, or irregular heartbeat, for the last 13 years. However, according to two of these four companies, this donor is at below-average risk for developing atrial fibrillation" (Direct-to-consumer genetic testing, 2010, p.33). A negative DTC genetic testing result with later development of the disorder may lead to feelings of confusion or anger as the patient is given false reassurance only to unexpectedly be given the diagnosis later on. If a patient were to currently have a genetic disorder only for a DTC genetic test

to tell them they were at low risk it may leave them with more questions as to why they had developed that disorder. The patient may feel confused and worried of a potential misdiagnosis. This emotional burden cannot solely be blamed on testing inaccuracy as the tests themselves can be accurate while still inconsistent with the presentation of the patient. It is easy to misinterpret these tests as diagnostic when most of the time they are simply testing one risk factor among many. The lack or possession of the risk factors tested for may not fully predict the presentation of disease in the patient as there are other risk factors at play that are untested such as environmental factors and undiscovered or untested genes that are thought to have a connection to the disease.

The psychological effects of inaccurate DTC genetic testing are evidenced in a 2013 study by Dar-Nimrod et al. This study gave randomized participants fake genetic testing results that told them they had an increased risk for alcoholism. The study found that these participants reported "reduced perceived personal control over drinking" after receiving the fake results (Dar-Nimrod et al., 2013, p.132). This study shows that DTC genetic testing can have psychological effects on consumers. When consumers are given such results they may take them to heart and start believing they are ill. Consumers may switch to a negative perspective where they are thinking more poorly of their health and noticing symptoms based on inaccurate results. This could act as sort of a reverse placebo effect.

Accurate DTC genetic testing results can also cause emotional trauma to consumers when the consumer is not properly prepared through a genetic counseling session to pursue testing and receive their results. A 2012 case study by Dohany et al. described the experience of a woman genetic counseling patient after unexpectedly

discovering she had a BRCA mutation through DTC genetic testing. The case study states, “After testing she presented for genetic counseling with anxiety, distress, and a deficit of knowledge about what the DTC genetic testing revealed” (Dohany et al., 2012, p.399). In the case study the patient was unprepared to receive her positive result due to the DTC genetic testing company’s lack of genetic counseling and the difficulty of the consumer being able to accurately comprehend the genetics statements found on the DTC genetic testing company’s website. As DTC genetic testing is so easily accessible and quick to purchase, consumers may not be giving themselves enough time to make an informed decision as to whether they truly want to know the results of these tests or if they are just in search of entertainment as was seen as one of the consumer motivations earlier examined. This leaves them unprepared emotionally to receive a positive result and leads to the anxiety, distress, and confusion that was seen in the case study.

### *Overuse of Healthcare*

DTC genetic testing may lead to the overuse of healthcare as patients undergo increased screening and diagnostic procedures based on inaccurate test results. Receiving a false positive DTC genetic test result may lead to an unnecessary utilization of genetic testing to confirm or dismiss the result. If one family member receives a false positive result from a DTC genetic test it could lead to multiple family members seeking out expensive genetic testing that they otherwise would not have needed to undergo.

The previously mentioned 2017 study by Lu et al. examined how DTC pharmacogenetic testing could lead to lowered healthcare spending in the long term (Lu et al., 2017). This study also explained, however, that the results of DTC pharmacogenetic tests do not have an immediate applicability for the patient as the

patient must be prescribed the drug whose effects were tested for in order for the results to be worthwhile. This means that the DTC pharmacogenetic tests may not have value to the patient or their physicians for many years until the medicine tested for is prescribed or it may never have value if the patient never develops a disorder that requires any of the medications tested. When taken at face value, DTC pharmacogenetic tests may be perceived as cost-ineffective as the results are useless if you are not prescribed any of the drugs being looked at. The tests may be considered a waste of money from this short-term perspective rather than a way to reduce healthcare spending.

Another previously mentioned study by Francke et al. in 2013 was used to describe the benefit of DTC genetic testing leading to improved health outcomes (Francke et al., 2013). The study shows how opening up the option of early intervention is a benefit of DTC genetic testing for consumers, but the study also shows how it can lead to unwanted or unnecessary interventions. The study states that after sharing results with their physician, "some female mutation-carriers expressed feeling pressured into surgical procedures by physicians" (Francke et al., 2013, p.11). Early intervention based on DTC genetic testing results, therefore, can also cause harm to the patient through undergoing serious surgical procedures that the consumer may not have actually wanted or needed, but felt the result required it of them.

DTC genetic testing may lead to unnecessary increased screenings and procedures that the patient and physician wouldn't have otherwise sought out. Based on the large amount of inaccurate test results that were shown to come from DTC genetic testing, it would be unwise and very costly if unnecessary increased screenings and risky diagnostic or preventative procedures were provided for everyone who received a positive result

from a DTC genetic test. A 2010 article by Annes et al. depicts this worry stating, "As the number of conditions for screening expands, so will the cost to our health care system and the risk of iatrogenic harm to patients" (Annes et al., 2010, p.1101). DTC genetic testing companies use many tests that are not in clinical use and therefore increase the amount of DTC tests at a faster rate than clinical genetic tests. This is due to the lack of regulations as is shown in 23andMe's use of polygenic risk scores to determine diabetes risk. "According to 23andMe, the current diabetes report needs no regulation at all. That is because it falls into an exemption for low-risk tests and phone apps that offer only 'general wellness' suggestions, not real medical advice or diagnoses" (Regalado, 2019, para. 14). As these poorly regulated tests are able to grow at a faster rate than clinical tests, the unnecessary and inaccurate screening for disease leads to an overuse of healthcare and increased healthcare spending costs.

# CHAPTER FIVE

## Current Regulations

Regulation of DTC genetic testing comes from a goal of enhancing perceived benefits of the tests for consumers and patients while mitigating the risks and harms. Regulations, such as the Clinical Laboratory Improvement Act of 1988, preceded DTC genetic testing. Additional regulations have been and are being continually established to protect the consumer from harm and improve their experience with DTC genetic testing, one of the most recent being California's Genetic Information Privacy Act that took effect January 1st, 2022 (Kadish & Schafer, 2022). The regulation of DTC genetic testing has significantly improved since the start of DTC genetic testing in 2002. Despite this improvement, there is still a need for continued improvement and additional regulations to close the gaps left by current regulations. The gaps in current regulation and the need for improvement will be discussed in the last chapter. This chapter will provide an overview of important regulations currently in place.

### *Clinical Laboratory Amendments of 1988 (CLIA)*

One of the first pieces of legislation involved in the regulation of DTC genetic testing began before DTC companies existed: the Clinical Laboratory Amendments of 1988 (CLIA). The Center for Medicare and Medicaid Services was given responsibility for regulating any laboratory testing of human specimens by CLIA in 1988. The purpose of the regulations implemented by CLIA is to ensure that laboratory testing on human specimens is being performed with accuracy and reliability.

The Center for Medicare and Medicaid Services explains the overview of laboratory developed tests (LDT), tests created and performed by a single lab, with the statement, "Under the CLIA regulations, when a laboratory uses a test system that has not received FDA clearance or approval, such as a LDT, the laboratory may not release any test results prior to establishing certain performance characteristics relating to analytical validity for the use of that test system in the laboratory's own environment" (Center for Medicare and Medicaid Services, 2013, p.2). This statement explains how tests that have not been approved by the FDA are not able to provide test results to patients before CLIA has investigated the analytical validity of its use. DTC genetic tests were not considered to fall under the FDA's jurisdiction until 2010, however, CLIA applied to DTC genetic tests during the timeframe between their development and when the FDA began regulating them. CLIA's jurisdiction of DTC genetic testing is more explicitly stated by the Center for Medicare and Medicaid Services stating,

> The CLIA regulations and standards do not differentiate between facilities performing DAT [Direct Access Testing also known as Direct to Consumer Testing] and facilities performing provider ordered testing. All facilities that meet the definition of 'laboratory' under CLIA must obtain an appropriate CLIA certificate prior to conducting patient testing, including DAT. These CLIA certificates must be maintained and the CLIA laboratory procedures must be followed throughout all phases of testing. (Center for Medicare and Medicaid Services, n.d., p.1)

CLIA oversees that the laboratories performing DTC genetic testing are up to the quality standards required to ensure analytical validity. CLIA's investigation of analytical validity entails an analysis of accuracy, precision, analytical sensitivity, analytical specificity, reportable range, reference interval, among other measures of the test's performance (Center for Medicare and Medicaid Services, n.d.). The analytical validity of the tests as

determined by CLIA only applies to the particular lab that is being observed as it is influenced by the specific conditions, staff, equipment and patient population of the specific laboratory (Center for Medicare and Medicaid Services, n.d.).

CLIA was one of the first regulators of DTC genetic testing and for many of the first years of the existence of DTC genetic testing it was the only regulator in place. CLIA upholds the expectation that the laboratory tests accurately detect what they are meant to detect. CLIA is not involved in determining how that detection relates to a clinical diagnosis or one's risk factor for any particular disease or condition. While CLIA oversees the laboratories performing DTC genetic tests, it does not provide any oversight in the clinical validity of DTC genetic tests or the interpretation and presentation of results of the CLIA certified tests to patients and consumers.

### *Genetic Information Nondiscrimination Act of 2008 (GINA)*

In 2008, President George W. Bush signed the Genetic Information Nondiscrimination Act (GINA), enthusing that the act protects citizens from the misuse of their genetic information while upholding the basis and purposes of health insurance companies ("The Genetic Information Nondiscrimination Act", 2009). GINA prevents health insurance companies and employers from requesting genetic information or discriminating on the basis of genetic information. Genetic information is defined in the act as, "family medical history, manifest disease in family members, and information regarding individuals' and family members' genetic tests" (National Human Genome Research Institute, 2022, para. 3).

Under GINA, companies that offer health insurance cannot require an individual to undergo genetic testing or provide the company with genetic test results. Health insurance companies are also prohibited from determining health insurance eligibility and making decisions in regard to coverage, premiums, and underwriting on the basis of an individual's genetic information (National Human Genome Research Institute, 2022). GINA applies to both private and public or government health insurers but is limited in its protections for the US Military's TRICARE Insurance program (National Human Genome Research Institute, 2022). GINA in the health insurance scope is implemented by the Internal Revenue Service, Department of Labor, and Department of Health and Human Services. In addition, GINA required an amendment to the Health Insurance Portability and Accountability Act of 1996 (HIPAA) to include genetic information in HIPAA's privacy protections of health information (National Human Genome Research Institute, 2022). In clinical research, GINA requires that consent forms include information on risks and confidentiality practices.

The protections against discrimination of genetic information provided by GINA includes prohibiting employers from making genetic testing or release of genetic testing results a condition of employment. GINA prohibits the use of genetic information in employer decisions on hiring, firing, promotion, pay, job assignment, or other employment related decisions (National Human Genome Research Institute, 2022). Under GINA, the volunteering of genetic information by employees to employee wellness programs cannot be used by employers to provide inducements such as discounts, paid time off, or penalizations. GINA extends to all employers excluding the US Military with at least 15 employees, as well as, employment agencies, labor

organizations, joint labor-management training programs, and apprenticeship programs (National Human Genome Research Institute, 2022). While GINA protects consumers from discrimination based on their genetic information by health insurance companies and employers, it fails to protect consumers of certain populations such as the military and does not protect against other insurance companies such as life insurance from discriminating using genetic information.

### *FDA Regulation*

The FDA has the legal authority to regulate "food, drugs, cosmetics, biologics, medical products and tobacco" (U.S. Food and Drug Administration, n.d. a, para. 1). One might expect DTC genetic testing to fall under the category of medical products or medical devices. The FDA defines a medical device as,

> An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is… intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals. (U.S. Food and Drug Administration, n.d. b, sec. 3)

However, during the first few years that DTC genetic tests were on the market, the FDA did not require approval for the marketing and production of these products as they were not considered to be "medical devices" (Direct-to-consumer genetic testing, 2010). Jeffrey Shuren, M.D. testified as a representative of the FDA in 2010 that, "A genetic test is subject to FDA oversight only if it is a medical device" (Direct-to-consumer genetic testing, 2010, p.68). In 2010 the FDA sent cease and desist letters to five genetic testing companies while regulations began being established. From 2010 onwards, DTC genetic tests were deemed to be medical devices needing FDA regulation. In 2013, more DTC genetic testing companies were sent cease and desist letters. As a result, some DTC

genetic testing companies closed. Companies that remained in business began a close relationship with the FDA as they cooperated in attempting to conform to the new FDA regulations. In 2015, carrier screening tests first received FDA approval followed by genetic health risk tests in 2017 and the first and only pharmacogenetic test in 2018.

The FDA's current regulations for DTC genetic testing require premarket review by the FDA for only certain types of tests such as cancer predisposition tests, while other types such as general wellness tests remain exempt from premarket review. All types of DTC genetic tests, however, have regulatory standards set by the FDA that the testing companies must meet relating to the development and marketing of DTC genetic tests. DTC genetic tests exempt from premarket review by the FDA include carrier screening tests, low risk general wellness tests, ancestry tests, and genetic health risk (GHR) tests developed by previously approved companies. DTC genetic tests requiring premarket review by the FDA include the first GHR test developed by a company, cancer predisposition tests, and pharmacogenetic tests (U.S. Food and Drug Administration, 2019).

Some of the regulatory standards for tests required by the FDA include providing adequate information to the consumer on a multitude of topics relating to the test, as well as conducting a study on how well users comprehend test results both before and after taking the test. The company must also provide an educational module and list of statements on the limitations of the tests. Information must be made prominently available to consumers through a hyperlink on the product and through any online website. The information that must be provided to consumers includes resources for accessing a geneticist and genetic counseling, clinical validity of the test, the gene

involved, guidelines for recommended testing or a statement declaring the test not professionally recommended, testing methods and procedures, prevalence of mutation in different ethnic and racial populations, risk mitigation efforts, test failure information, test interpretation information, accuracy statistics, positive and negative predictive values, specificity, sensitivity, odds ratios, likelihood ratios, precision, definitions, and the option to accept or decline to receive specific test results (U.S. Food and Drug Administration, 2022).

### *State Legislation*

Many states have passed additional legislation to supplement federal regulations on DTC genetic testing. In 2021 alone seven states passed new legislation aimed at protecting the privacy of consumer genetic information, one of the most recent being California's Genetic Information Privacy Act that went into effect on January 1st, 2022. Alaska and Nevada were among the first to implement state legislature on genetic privacy in previous years (Claypoole & Ey, 2021). The seven states that passed new legislation in 2021 included Arizona, California, Florida, Maryland, Montana, South Dakota, and Utah (National Conference of State Legislatures, 2021).

State laws cover a variety of different scenarios involving DTC genetic testing. Some states passed legislation related to limiting law enforcement's use of DTC companies for forensic genealogy. South Dakota's new legislation extends GINA by prohibiting life insurance companies and long-term care insurance companies from discriminating based on genetic information. California and Utah both enacted different versions of a Genetic Information Privacy Act (GIPA). Florida enacted the Protecting DNA Privacy Act.

California has some of the most expansive and recent regulations concerning DTC genetic testing. The Genetic Information Privacy Act of California (GIPA) was designed to provide citizens with greater protection from breaches in genetic privacy by DTC genetic testing. GIPA declares DTC genetic testing to be any situation where the consumer initiates genetic testing or a healthcare professional initiates genetic testing for reasons other than medical diagnosis or treatment, as well as, any company that collects, uses, or maintains data obtained from a DTC genetic testing company (Wyrick et al., 2021). Exceptions to acquiring DTC genetic testing company status include if the data is de-identified, if the data is being used for research by post-secondary education institutions and is assured with the Department of Health and Human Services, and genetic information that is covered under California's Confidentiality of Medical Information Act (Wyrick et al., 2021).

GIPA requires DTC genetic testing companies to follow regulations involving explicitly explaining privacy information and procedures to consumers, acquiring consumer consent for multiple stages of data collection and storage, reasonable security measures, protection of consumer rights such as the right to withdraw consent and access raw data, and agreements between third parties and the company as to the use and practice of providing genetic data to the third parties (Wyrick et al., 2021). GIPA also prohibits discrimination by DTC genetic testing companies of consumers on the basis of them exercising rights outlined by GIPA; the disclosure of genetic information to those in charge of deciding on health insurance, life insurance, disability insurance or employment; and the inference of consumer consent on the basis of nonaction (Wyrick, Robbins, Yates & Ponton LLP and Meeks).

Florida's Protecting DNA Privacy Act is similar to California's GIPA in the areas of expressly requiring consent and limiting third party use of genetic data (Claypoole & Ey, 2021). Florida and California's laws differ in enforcement where California applies civic penalties while Florida applies criminal penalties (Claypoole and Ey, 2021). Utah's version of GIPA highlights very similar regulations to California's GIPA (*SB0227*, n.d.).

# CHAPTER SIX

## Gaps in Current Regulation and the Need for Improvement

Current federal and state regulations of DTC genetic testing leaves many gaps open that could cause harm to consumers. While CLIA works to ensure laboratories are accurately performing tests, they do not ensure that the tests themselves provide accurate interpretations and applicability to health. While GINA protects from discrimination based on genetic information by health insurance companies and employers, it does not protect against discrimination by disability or life insurance. While the FDA requires preapproval of the first genetic health risk test by a company, any tests afterwards are free to go on the market without first being reviewed. While state legislation works to close the gaps left by federal regulations, each state may not be as proactive in this regulation as others. There is a need for improvement upon current federal regulations of DTC genetic testing to protect consumers from potential harms and enhance the benefits gained from DTC genetic testing.

### *CLIA*

The Clinical Laboratory Amendments of 1988 regulate the laboratories that perform DTC genetic testing to ensure that the laboratory tests are accurately detecting what they are designed to detect. This is known as "analytical validity" which is what CLIA focuses on. CLIA does not however regulate or investigate how these tests are interpreted and whether they accurately describe the presence of a disease. This is called "clinical validity". CLIA states on their website that,

> Further, CMS' CLIA program does not address the clinical validity of any test – that is, the accuracy with which the test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in a patient. On the other hand, FDA evaluates the clinical validity of a test under its premarket clearance and approval processes and as a result, has expertise in this area. In other words, the FDCA encompasses clinical validity whereas CLIA does not. (Center for Medicare and Medicaid Services, 2013, p.2)

The gap in regulation of clinical utility that is left after CLIA is supposed to be filled by the FDA's regulations. The Center for Medicare and Medicaid Services is in charge of enforcing CLIA acknowledges, however, that the FDA uses enforcement discretion in many DTC genetic tests (Center for Medicare and Medicaid Services, 2013). Enforcement discretion means that the FDA has the jurisdiction and authority to regulate DTC genetic tests on their clinical validity but chooses not to do so. Therefore, the intention of cooperation between the Center for Medicare and Medicaid Services and the FDA to cover both analytical and clinical validity in their combined regulations is unsuccessful as the FDA does not complete the regulation of clinical validity. There is a need to improve FDA regulations of DTC genetic tests in order to complement CLIA as intended.

### *GINA*

The most obvious gap that the Genetic Nondiscrimination Act of 2008 leaves in regulation of genetic privacy is that it only applies to health insurance companies and employers. There are no federal regulations in place to prevent other entities such as life insurance companies, disability insurance companies, and long-term care insurance companies from discriminating based on genetic information. While some states such as

South Dakota have filled this gap with state legislation, there are still plenty of states where this gap is left open.

GINA also does not apply to the U.S. Military nor the Indian Health Service. A 2008 article on the military's use of genetics states, "All U.S. service members, including active duty and reserve military personnel, must provide a DNA sample that may be used to identify their remains should they die in battle" (Baruch & Hudson, 2008, p.439). The article also explains the U.S. Military's testing of employees for the genetic disorders sickle cell anemia and Glucose 6-phosphate dehydrogenase deficiency. If a member of the military tests positive for one of these disorders, they can be restricted from being placed in environments or jobs that exacerbate the illness. They may also wear red armbands to alert their superiors of an intolerance of strenuous exercise. The U.S. Military has worked to decrease genetic discrimination in their policies. One policy that was adjusted in response to GINA, was the policy on injury or illness incurred in the time of duty which would provide special disability benefits. Originally this policy excluded genetic disorders from being incurred during the time of duty. The 2008 article on the military's use of genetics presented a case where,

> [A] Marine Corps drill instructor who was diagnosed with cancer after 15 years of service was denied healthcare and disability benefits after he was determined to have Von Hippel-Lindau syndrome, a genetic condition. Benefits were reinstated once he successfully argued that the underlying condition may have been exacerbated by environmental exposures during his tours of duty. After this case, DoD [Department of Defense] permitted benefits to be awarded in cases of genetic disease if a service member had completed at least eight years of active duty. (Baruch & Hudson, 2008, p.440)

The policy has been changed to now consider genetic disorders where symptoms had not yet developed at the time of entrance into the military but had developed before discharge and genetic disorders that had been present at entry but service exacerbated symptoms to

both be considered as incurred in the time of duty and subject to disability benefits. While the military policy has covered this gap rather well, the protections are still not as expansive and ensured as those covered under GINA as a policy is less stable than legislation.

A gap is also left in GINA in its application, or lack thereof, to employee wellness programs. Employers may request employees to voluntarily provide genetic information for the sake of employee wellness programs implemented by the company. Employers may not, however, provide incentives or penalties for the voluntary participation of employees. This was amended in the case of spousal genetic information,

> On May 16, 2016, EEOC amended GINA regulations to provide clarification on the issue of spouses' genetic information. This amended rule states that it is permissible for wellness programs to offer limited inducements, in the form of a reward or penalty, in exchange for information about the manifestation of disease or disorders in spouses. (National Human Genome Research Institute, 2022, para. 14)

While GINA includes family member health information including that of spouses to fall under the protected genetic information of an individual, this is contradicted in an amendment allowing incentives and penalizations for the volunteering of spousal genetic information in regards to employee wellness programs.

While some states have been striving to fill the gaps left by the federal regulations provided by GINA, there is a need for greater uniform federal regulations to fill these gaps across the board. There is a need for regulation regarding life insurance, disability insurance, and groups left out of GINA such as the military and Indian Health Services to further protect citizens from discrimination based on their genetic information.

### *FDA Regulation*

As mentioned in the section on gaps in CLIA, the Food and Drug Administration leaves gaps in regulation using enforcement discretion. FDA regulations require a premarket review of only certain types of DTC genetic tests that the FDA has deemed to be high-risk. This leaves DTC companies the ability to market and sell tests falling under the other categories with no regulation or repercussions until a problem with it is brought to the FDAs attention. For example, 23andMe's test for type 2 diabetes using polygenic risk scores was classified as a "general wellness test" and therefore was exempt from FDA regulation (Regalado, 2019, para. 14). While the science and accuracy of polygenic risk scores are highly criticized by researchers and professional institutions, 23andMe is able to sell tests based on polygenic risk scores without any oversight. The FDA does not regulate ancestry tests or low risk general wellness tests. While ancestry tests may not fall under the classification of a medical device by the FDA, general wellness tests could be considered medical devices due to the intention of preventing disease. Therefore, while general wellness tests might fall under the FDA's jurisdiction, the FDA is choosing to exercise enforcement discretion to not regulate them. The FDA does not require premarket review for any carrier screening tests, nor for genetic health risk tests after the company has received approval in premarket review for their first genetic health risk test. This leaves a large gap in regulation as many of the tests within the FDA's jurisdiction to regulate are being left unregulated.

The lack of uniform standards across companies in what is considered low risk as opposed to high risk and which genes are relevant to include in testing is another gap in FDA regulation. During the 111th Congress in 2010, a 23andMe representative stated,

> [T]here are different standards for inclusions of which SNPs are looked at and what weight is given to them. And there are differences among which variants can be tested among the technologies that are used by the different companies. So we agree that it is not acceptable to get the different results and that we need standards. We have written a letter to the head of NIH and FDA requesting their help. We have worked with our colleagues and will continue to do that to set these standards. (Direct-to-consumer genetic testing, 2010, p.157)

While DTC companies claimed during the 111th congress that they were willing to work with the FDA to establish uniform standards in their tests, the FDA has yet to set any such standards (Direct-to-consumer genetic testing, 2010). The lack of uniform standards across companies is evident in a statement currently expressed on the FDAs website, "Not all direct-to-consumer genetic test companies test for the same set of variants, and therefore may provide different results for the same disease or condition" (U.S. Food and Drug Administration, 2019, para. 5). This lack of standards in determining test results is a gap in FDA regulation that leads to unreliable results in DTC genetic tests as one company may display an individual to be at low risk while another company may claim that same individual is at high risk for a certain disease.

Another area for improvement in FDA regulations is the involvement of genetic counselors in DTC genetic testing. The regulations of genetic health risk tests and of carrier screening tests require DTC companies to provide information on how to access a molecular geneticist or a genetic counselor. While this is an important regulation to be in place, it lacks providing patients with information on who genetic counselors are and what an appointment with one would look like. Patients may not be inclined to take advantage of such resources without awareness of what they entail. Genetic counselors are specifically trained in patient education and counseling on the emotional burden of genetic testing and diagnosis. Increasing genetic counselor involvement in website

development or providing genetic counseling services would be a necessary enhancement to DTC genetic testing companies.

Both genetic health risk and carrier screening FDA regulations require a multitude of pages and statements describing everything from the limitations of the test to the procedures of the test itself. While this information is all necessary, it may be overwhelming to patients and patients may be inclined to skip through reading the information. There should be a system in place to prevent patients from skipping through information about test limitations, risks, and resources. One suggestion could be a video format that must finish before the result is shown. Another option may be a quiz on the information that must be passed before the result is given. This would ensure the patient properly understands the necessary information and can adequately provide informed consent to receive their results. While the FDA requires the DTC genetic carrier screening and genetic health risk tests to undergo comprehension studies to ensure the patients in the study can correctly understand the information provided, there is nothing in place to ensure the everyday patient will actually read the information in the first place.

The FDA leaves gaps in their regulation by not reviewing all types of DTC genetic tests before they reach patients. There is a need to extend FDA premarket review to carrier screening tests and individual genetic health risk tests. While some may argue that a requirement to review all tests beforehand leads to long wait times for approval which stifles innovation, the consumer's safety and right to accurate test results must come before the desire for swift innovation. Finally, there is a need to improve consumer understanding through increased involvement of genetic counselors and a less easily dismissed medium for providing important testing information.

*Additional Areas for Improvement*

Unregulated DTC genetic testing led to a state of disarray when companies provided inconsistent results to ill-researched tests. Consumer motivations displayed the desire for DTC genetic testing and the personal purposes behind pursuing DTC genetic testing. There are shown to be many potential benefits both to public and personal health from DTC genetic testing. These benefits combined with consumer motivations and desires to pursue DTC genetic testing establish that DTC genetic testing should not be abolished, but reformed. The potential benefits should be kept in mind in this reforming of DTC genetic testing so as not to thwart the benefits with excessive regulations. The potential risks involved in DTC genetic testing have alarming consequences and show the need for intentional regulations to mitigate harm to consumers. In the years since DTC genetic testing began, many regulations have been implemented to help prevent harms and risks while increasing benefits of DTC genetic testing. These regulations have significantly improved the accuracy and patient understanding in DTC genetic testing, however there are still gaps formed in these regulations. The intentions behind CLIA and FDA regulations working in a complementary manner are not being met due to a lack of oversight by the FDA. The FDA must increase their review of DTC genetic tests before they are allowed on the market to reconcile this intention of being complementary to CLIA. GINA leaves it up to the states to fill in the gaps of genetic discrimination by life, disability, and long-term care insurance. GINA also does not extend to populations including the Indian Health Services and the military. There is a great need for federal legislation to fill in the gaps left by GINA and provide uniformity among all states in the protection of the privacy of one's genetic information. Lastly, there is an urgent need for the implementation of standards across DTC genetic testing companies to eliminate the

conflicting high and low risk test results from differing companies and improve the accuracy of DTC genetic tests. Whether this be implemented by the FDA or some other regulating entity, standards must be decided upon and test results across DTC genetic testing companies must be made cohesive.

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