

Direct-to-consumer genetic testing:
Where we are and where we could be

A Plan B Paper

In Partial Fulfillment of the
Master of Science in Science, Technology and Environmental Policy
Degree Requirements
The Hubert H. Humphrey School of Public Affairs
The University of Minnesota

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May 24, 2016

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Date

I. Introduction

“The future of medicine has arrived! Receive personal treatment based on your own, unique genetic code.” This is the message that new biotechnology companies, like 23andMe, are advertising to the public. Their main product is the direct-to-consumer (DTC) genetic test, where for a low fee and a small sample of an individual’s cheek cells, a person can receive a report displaying their increased risk for common diseases and chronic conditions. These companies are filling a niche market that is also consistent with President Obama’s Precision Medicine Initiative (White House, 2015). But is the technology and its results as promising as they claim? Personalized treatment with genetic-based components may be the medicine of the future, but is society ready for it? With members of the United States Congress in mind, this paper will examine whether the United States has the proper governing structure or approach to effectively regulate direct-to-consumer genetic tests. It will also explore how a balance can be obtained, given the current costs and benefits to society, between scientific innovation and decreasing risks to the consumer. Finally, this paper will give a background of the technical side of direct-to-consumer (DTC) genetic tests, the costs, benefits, risks, and concerns of different aspects of DTC tests, alternatives to effectively regulate DTC tests, and a comprehensive recommendation.

II. Methodology

While genetic tests for diagnostic and prognostic purposes are relatively new biotechnological innovations, some form of them has been around for decades. One of the first applications was testing newborns for phenylketonuria in 1965 (MDH, 2016), a genetic disorder that leads to the build-up of phenylalanine in the body (Mayo Foundation, 2014). A genetic

mutation in a gene that rids the cell of phenylalanine causes it to accumulate inside the cell (Mayo Foundation, 2014). This can lead to severe neurological disorders if not detected early (Mayo Foundation, 2014). However, following a diet of limited phenylalanine reduces the amount of phenylalanine in the body. Thus, there is much less to build up inside the cell, reducing symptoms of the disease. Introducing the “PKU test,” or “heel-stick test,” for newborns allowed physicians to detect the mutation and recommend a diet for the infant to prevent symptoms due to phenylalanine build-up. Using a small amount of blood during a “heel-stick” within a couple days of an infant being born allowed for this type of testing and medical intervention. Since then, the newborn screening test has expanded to cover many treatable genetic disorders. In Minnesota, the newborn screening test includes the analysis of 50 genetic disorders that are treatable with early intervention (MDH, 2016).

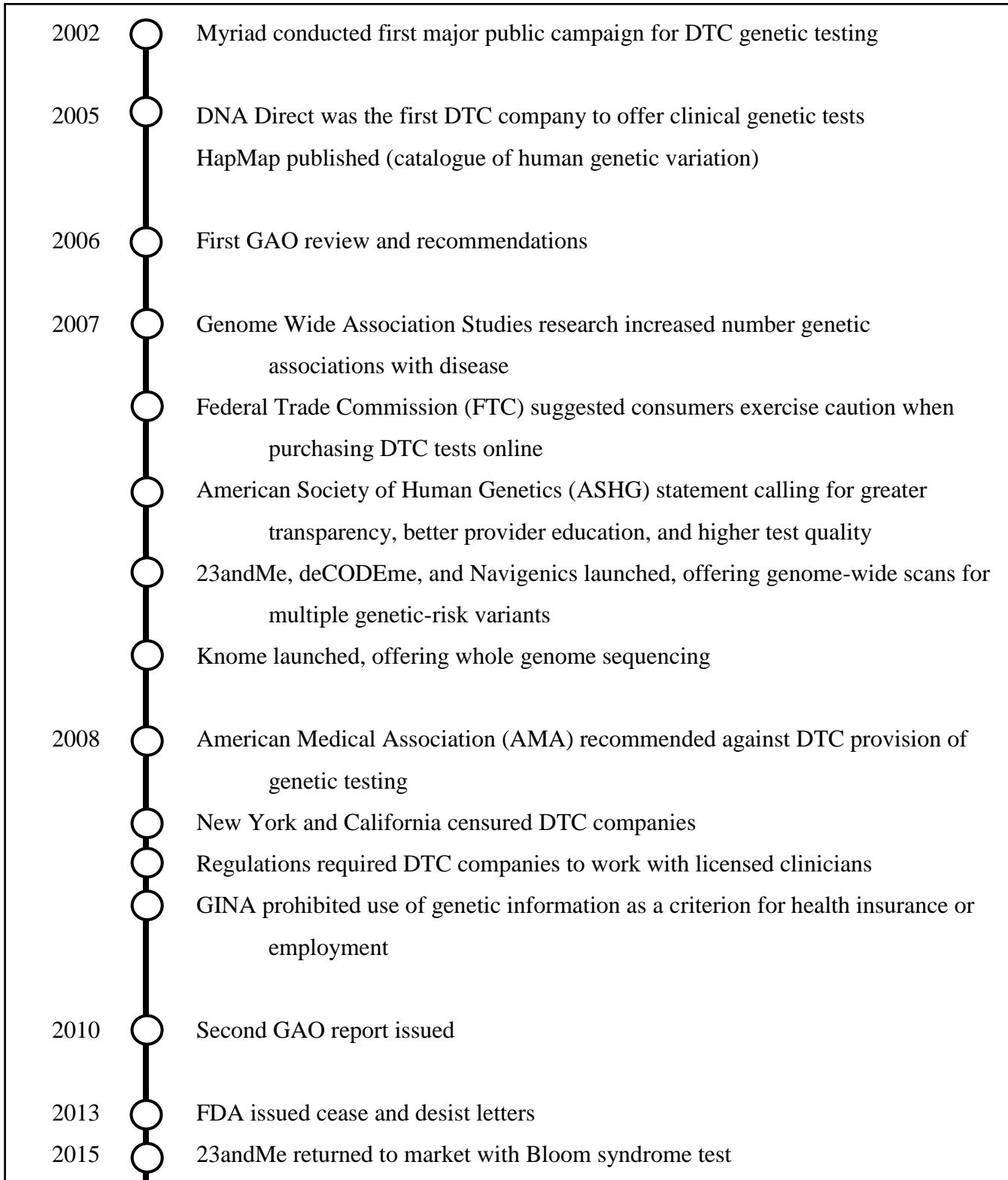
Understanding and knowledge of genetic diseases and their molecular causes continues to increase at a fast pace. However, the medical field still lacks the preventative measures, curative means, or treatments for many genetic disorders (Liu and Pearson, 2008). After the Human Genome Project was completed in 2003 and HapMap published in 2005 (Figure 1), there was an increased effort to associate traits and diseases with genetics (McBride et. al, 2010). The completion of the Human Genome Project has been shown to be very insightful for the increased likelihood of obtaining clinical benefits from new genetic technologies (Liu and Pearson, 2008). Following the completion of the Human Genome Project, the cost of sequencing a genome has decreased from billions of dollars to a few thousand (Caulfield and McGuire, 2012). The ability to sequence specific genes or genomes more inexpensively allows researchers to make gene-trait associations more quickly and easily. When translated to medicine, there is the potential to understand more complex genetic disorders and develop a cure or treatment more quickly. What

used to be reserved to a physician's office for symptomatic patients or a patient with a significant family history for disease is becoming more accessible through the use of direct-to-consumer genetic tests. Using the Internet, genetic tests for 1200 diseases can be found (Liu and Pearson, 2008).

Direct-to-consumer genetic tests use the technology of clinical, laboratory tests to diagnose disease and package them conveniently so that a consumer can collect a sample in the comfort of their own home and send it to a third-party laboratory to analyze. They are unique in that they span across multiple economic sectors. Direct-to-consumer genetic tests can be diagnostic and prognostic, placing them in the medical/health sector. These genetic tests can also be used for curiosity or entertainment purposes, through ancestry tracing for example. Genetic tests can be one of five types – relationship testing, pseudo-medical testing (e.g. nutrigenetics¹), recreational genetics, disease/disease susceptibility, and polygenic susceptibility. Relationship testing is mainly used for simple paternity testing (Trent, 2012). Pseudo-medical genetic testing focuses on using an individual's DNA information to create dietary strategies and supplements to improve the individual's well-being (Trent, 2012). The field of nutrigenetics is promising for individuals suffering chronic illness due to undiagnosed nutrient metabolism issues, but there should be great caution when the company performing the testing is the one also offering expensive supplements claiming to be based on DNA information. Recreational genetic testing is popular for tracing ancestry (Trent, 2012). However, there is the potential for a direct-to-consumer genetic test used recreationally to evaluate whether a child has certain desirable traits, like assessing athletic ability (Trent, 2012).

¹ Nutrigenetics – Utilizing DNA information and dietary strategies to improve health and well-being (Trent, 2012)

Figure 1. Timeline of selected dates from literature sources depicting important events in the history of direct-to-consumer genetic testing (McBride et. al, 2010; Trent, 2012; U.S. FDA, 2015).



Disease and disease susceptibility testing is performed in conjunction with genetic counselling and available in a clinical setting (Weaver and Pollin, 2012). The test usually involves examining a genetic variant with an observable and correlational effect (Weaver and Pollin, 2012). Direct-to-consumer genetic tests can be well-utilized for these types of straight-forward one gene-one disease genetic disorders. Direct-to-consumer genetic tests have a large draw in those interested in examining polygenic susceptibility, diseases that involve more than one gene and/or effects from the environment. Due to the complex and lesser-understood mechanisms of complex diseases (e.g. heart disease and Type II diabetes), these tests are usually not offered in a clinical setting (Weaver and Pollin, 2012). Therefore, given the lack of correlation effect on a health condition, the disorder is no longer one gene-one disease, and is sometimes too complex to offer any insight into treatment of the disorder (Weaver and Pollin, 2012). However, DTC companies can still attempt to assign a risk level based on genetic data and a health questionnaire, thereby attempting to link multiple genetic factors to common disease.

Most direct-to-consumer genetic tests ordered via the Internet send a kit with instructions on obtaining and submitting a sample for analysis. Some are as easy as using the provided swab to rub along the inside of the individual's mouth or spitting into the provided tube, collecting DNA-rich cheek cells. Once submitted, the company claims to assess the individual for susceptibility to common chronic conditions, like diabetes or heart disease, based on single nucleotide polymorphism (SNP²) associations that have been reported in genome-wide association studies (GWAS) (Weaver and Pollin, 2012). However, SNP associations are still being studied, and are often limited to the population that comprises the sample of the study (Weaver and Pollin, 2012). Also, SNP associations explain less than 10% of the genetic

² Single nucleotide polymorphism (SNP) – A variant in only one letter of a gene sequence that may or may not have a correlational effect with a particular health condition.

component of the condition, even when all associated SNPs are combined (Weaver and Pollin, 2012). The largest potential benefit is the empowerment of the consumer to evaluate their genetic data report and potential risk factors to make healthy lifestyle changes.

Despite this large potential in personalized medicine, though, and the lack of peer-reviewed literature regarding effectiveness, these tests must be met with skepticism. Based on the literature, the risks for direct-to-consumer tests fall into four categories – company marketing, testing process, clinical validity, and interpretation of results – that will be discussed in this paper. Each of these is a possible intervention point for potential policy change. Given the fact that the entire genome is not yet fully understood, concerns still need to be addressed regarding testing for preventable diseases (e.g. carrier status), versus treatable disorders (e.g. phenylketonuria), versus incurable diseases (e.g. Huntington’s and Alzheimer’s disease).

Risk Assessment Challenges

New technology comes with a set of unique risks, and direct-to-consumer genetic tests are no exception. Some risks stem from the lack of understanding of probability and uncertainty on the part of the consumer. Regarding direct-to-consumer genetic testing, risks include:

- Learning undesired information
- Lack of security with private, genetic information
- Not understanding or misunderstanding the results (leading to inappropriate follow-up care)
- Testing error(s)

These risk factors are important to consider when developing a policy for DTC tests. Policy decisions have far-reaching consequences for DTC tests given the number of stakeholders involved, the extent to which DTC companies span, and the amount of sensitive and private data obtained from a person. Cultural values and personal morals also play a factor when a person contemplates undergoing a direct-to-consumer genetic test.

One way to describe risk is the probability that a hazard will lead to an undesirable outcome or an expected loss (Fatehi, 2015). Another way to describe risk is probability multiplied by the hazard. In the case of direct-to-consumer genetic tests, undesirable outcomes, expected losses, or hazards include:

1. Unwanted information
2. Inaccurate or ambiguous information, and/or
3. Emotional trauma following interpretation of the test results.

These hazards are subjective in nature and the fact that risk of harm is also influenced by past experiences, environmental factors, and other outside variables, it makes assessing risk more difficult in the DTC context (Weaver and Pollin, 2012).

In addition to an understanding of risk assessment, medical professionals and average consumers must also understand the technological capabilities of DTC genetic tests, uncertainty, probability, and genetic principles. Terminology, framing (language), and the use of ratios, relative risks, proportions, visual aids, and etc. (presentation styles) can considerably influence how an individual understands and contextualizes the presented information (Caulfield et. al, 2010). Probabilities can be calculated for diagnostic purposes, but predicting a future diagnosis involves uncertainty measurements and judgments based on experience from the analyst (Paul et.

al, 2014). Probability and uncertainty are concepts that even though objectively calculated, human judgment and perception can alter the value(s) to support or not support a certain belief (Morgan and Henrion, 1990). These judgments can be influenced by the ability with which an individual can recall previous occurrences or imagine the event occurring. By knowing the process of a certain event, individuals will still tend to make judgments based upon how results *appear* (Morgan and Henrion, 1990). For example, people know that the results of a coin toss are random, but will still judge the string of results HTHTTH to be more likely than HHHTTT or HTHTHT because the first string *appears* more random (Morgan and Henrion, 1990). However, as more experienced professionals know, all three strings of results are equally as likely (Morgan and Henrion, 1990). In the DTC context, an example is a variant related to cardiovascular disease that can reportedly increase the risk for an individual developing the disease from 1.0% to 1.6% (Caulfield and McGuire, 2012). While it can be claimed to be a 60% increase, it is actually meaningless from a health and statistical perspective because 1.6% compared to 1.0% is still an extremely low risk of developing cardiovascular disease (Caulfield and McGuire, 2012). This example also serves to demonstrate the power of language and presentation when displaying risk, probability, and uncertainty. Therefore, while it is unknown whether a DTC company expresses risk in this fashion, the capability to do so does exist. When an individual does not completely understand that statistics and probability are estimates that *represent* risk, they will most likely re-interpret those values based on their own personal experiences (Caulfield et al., 2010).

Methodology of this paper

Understanding of this topic as well as developed alternatives and conclusions were formed using research and analytical methodologies. Research of topics surrounding direct-to-consumer genetic tests chiefly involved a search of primary literature sources. Company and agency-specific websites were also utilized to gain more understanding of information not published in journals. Finally, a small number of interviews were conducted with professionals currently practicing in the DTC genetic field. Interviewees included a genetic counsellor, a pediatric clinician, and a regulatory official for the United States Food and Drug Administration (FDA). The Bardach 8-step approach to policy analysis was used for the analytical methodology.

III. Current governance framework

Proponents and opponents of regulations surrounding direct-to-consumer genetic tests should work together to mitigate uncertain risks. Stakeholders for DTC tests include physicians, genetic counsellors, and other health professionals, patients/consumers and their relatives, researchers of new genetic associations, and genetic test developers. Policy intervention points can occur at different levels with differing stakeholders to identify areas where gaps occur, for example. Alternatives that allow for continued innovation, another evaluation criteria, are important so that genetic discoveries and treatments are not halted. Also, direct-to-consumer genetic tests are complex and that a one-size-fits-all approach is ineffective will be beneficial when developing alternatives and recommendations. Aspects of flexibility, adaptability, and good stewardship will be important for DTC test policies and regulations going forward. Finally,

an approach where there is open dialogue between stakeholders, creating a new type of governance structure will result in increased public trust as well as more effective policy.

Opinions of Professional Organizations

Several professional organizations have made their opinions quite clear. For example, the American Congress of Obstetricians and Gynecologists argued that direct-to-consumer genetic tests should be considered medical tests (ACOG, 2008). The organization asserted that results have significant impact on the future medical care of an individual as well as clinical decision making (ACOG, 2008). Furthermore, the ACOG argued that testing should only be performed after consulting with a qualified health care professional (e.g. genetic counsellor or medical geneticist) (ACOG, 2008). Not only will consumers/patients need counselling prior to testing, but the ACOG advocated that DTC genetic testing will create needs for counselling, support, and care after testing, too, especially for those individuals identified as carriers (ACOG, 2008). As a whole, the ACOG discouraged the use of DTC genetic tests because of the potential harm due to misinterpreted or inaccurate results (ACOG, 2008). Pregnancy tests are sold over-the-counter, and have the risk of being misinterpreted. However, follow-up confirmation testing at a clinic and counselling with a medical professional is necessary for later clinical decision making due to the complexity that is involved in a pregnancy. The same care and follow-up should be applied to direct-to-consumer genetic tests, too, according to the ACOG.

Other professional organizations, like the Secretary's Advisory Committee on Genetics, Health, and Society, American College of Medical Geneticists, American Medical Association, and American Society of Human Genetics, made similar recommendations (Appendix A)

(Caulfield and McGuire, 2012). Each organization stated recommendations from its unique point of view, guidelines for the federal level, for the company, and communication with consumers. For example, the American Medical Association (AMA), an organization for physicians, had recommendations involving professionals in the testing, advising on test marketing, informing consumers about the tests and privacy, and that federal oversight would include ensuring that company claims are truthful (Caulfield and McGuire, 2012). Overall, all four organizations recommended some form of federal oversight, consumer education, and acknowledgement of gaps in regulations and test limitations.

IV. Costs, benefits, risks, and concerns of direct-to-consumer genetic testing

Direct-to-consumer genetic tests have benefits on the individual consumer level as well as at the greater public health level. They also have a wide breadth of concerns, from the testing process to the greater implications of result interpretations. Costs of the concerns and benefits are difficult to define as many are intangible and subjective to the consumer. Major concerns surrounding DTC genetic tests involve clinical validity, company claims and marketing, the testing process, and interpretation of results. Concerns that will be introduced include privacy and ethical considerations.

Direct-to-consumer genetic tests have a unique set of risks and concerns, as well. The FDA has identified concerns with laboratory developed tests, within which direct-to-consumer tests can be included. These include unsupported claims from the company, erroneous results due to the lack of quality controls, and falsification of data (U.S. FDA, 2015). Concerns

addressed by this paper include clinical validity, company claims and marketing, the direct-to-consumer genetic testing process, and concerns surrounding interpretations of the results.

Benefits

Aside from the large strides in innovation and biotechnology, direct-to-consumer genetic tests have many benefits. One benefit is the ability of a consumer to purchase the technology at a low cost (e.g. \$199 through 23andMe (23andMe, 2016)), conduct the test at his/her home, and receive results without a referral from a physician. Consumers can then choose how their data will be used, and whether or not to include it as part of their medical record. Another prominent benefit is the increased personal knowledge for the consumer. This increased knowledge can lead to a sense of empowerment to be more proactive over lifestyle choices (Bollinger et al., 2013). A final public health benefit is the increased population knowledge; each piece of genetic data that is added to a shared database helps lead to future genetic discoveries and disease treatments, if it is shared by consent of the consumer.

Company Claims/Marketing

The market may be relatively small (Caulfield and McGuire, 2012), but there is still a great deal of concern surrounding the marketing of DTC genetic tests. It has been argued that since DTC testing is a part of general commerce, the communication of information to consumers is to simply promote the sale of lawful products and services (Messner, 2011). The lack of regulation allows for DTC tests to be on the market without rigorous quality assurance measures. Consumers, therefore, have informed choice and do not need to provide informed

consent³ (Messner, 2011). Informed choice is based on the information disseminated by the DTC genetic testing company, and what the consumer utilizes when deciding whether or not to pursue DTC genetic testing and the corresponding tests. Informed consent, on the other hand, involves a consumer's full understanding of the extent of the genetic testing performed by the DTC company. But do consumers truly understand the options placed in front of them to make the best choice for them? If claims are found to be unsupported by current science, thus making the testing choice and subsequent results more ambiguous, it could feasibly decrease the trust of the public in the real scientific and medical promise of genetics (Weaver and Pollin, 2012).

With limited regulations, the consumer must rely on the information provided in a company's disclaimer on their website. Information can also be presented in a way that veils the limitations of test(s), or with language more complex than the average consumer understands. Therefore, consumers may not question how or why the company claims certain attributes and measures about their tests. Companies often overstate the power of their DTC tests; that the results will predict a specific outcome. It is a common misunderstanding that the results of *predictive* genetic testing will determine a *definite* knowledge about the future (Liu and Pearson, 2008). True, there are genetic disorders that can be predicted by a targeted genetic test, but these are rare disorders that have only one gene associated with them. Most DTC tests are less targeted in that they are testing mostly asymptomatic individuals, so there is no gene-trait correlation in question. Combined with the company's desire to profit off of the number of their DTC tests sold, the result of the ambiguous and enthusiastic statements on company websites can be unfounded or contradicting risk measurements across different companies.

³ Informed consent involves the disclosure of risks and benefits in human subject research and clinical practice (Messner, 2011).

Customer reviews from the company website of 23andMe highlight this concern (23andMe, 2016). See Appendix A for the full text of selected customer reviews. The selected reviews highlight the knowledge gap between consumers purchasing the tests and the company providing a complete description. Of the selected reviews, most customers expressed dissatisfaction with the level of detail of the genetic component of their test (23andMe, 2016). Two reviews stated that results told them what they could already observe by looking into a mirror (23andMe, 2016). One review expected to receive results to advise him/her on the types of food to eat and the type of exercise that is best for him/her (i.e. nutrigenetics), and was disappointed to only receive information on the types of earlobes he/she had (23andMe, 2016). Only after complaints did the company clearly state their tests' limitations and the fact that many genetic diseases are complex with environmental influence (23andMe, 2016). Three reviews expressed interest in learning their risk for diseases like Alzheimer's, cancer, and diabetes, and were frustrated when they did not receive results related to those diseases (23andMe, 2016). The company responded that 23andMe "...[does] not offer reports on hereditary risks for diseases like cancer, heart disease, and other serious health risks" (23andMe, 2016). The most surprising review was a statement that the consumer bought the test for medical reasons, but had to pay an additional \$350 to follow-up with their physician (23andMe, 2016). It demonstrates an expensive consequence due to the misunderstanding between the consumer and DTC company. These reviews are examples of the miscommunication and misunderstanding between companies providing the technology and the consumers utilizing it. Displaying information and disclaimers more clearly and in plain language could go a long way in helping consumers have a better understanding of the potential and limitations of the product they are purchasing.

Interestingly, there is often little known about the attitudes and motivations of consumers to use direct-to-consumer genetic tests (Paul et. al, 2014). The few studies that have been done are fairly non-representative and not robust enough to draw significant conclusions (Paul et. al, 2014). This issue is compounded by the fact that consumers can greatly vary with social and cultural contexts (Paul et. al, 2014). A few motivations have emerged from the literature, however, which include curiosity, anxiety, and/or worry about their future health or that of a loved one (Paul et. al, 2014). A more profound and predominant reason is the empowerment over an individual's health through increased knowledge. In fact, many believe they have a right to know about their personal genetics and the impact that a diagnosis from such a test will have on their life (Paul et. al, 2014).

Testing Process

First, a test must be scientifically valid, sensitive and specific, avoiding false positives and negatives (Liu and Pearson, 2008). It must also be analytically valid, or accurate, targeting the correct gene/variant (Hudson et al., 2007). The testing process itself contains many areas where a policy intervention can occur, including the collection, storage, and processing stages. Areas that may be protected by company trade secrets include the array of SNP variants used and the analysis algorithms. Therefore, since there are multiple intervention possibilities, determining what stage would be most effective to implement regulatory action is difficult. Furthermore, there is still the potential for human error at any of these stages (since humans will ultimately design, implement, and operate machinery and protocols).

Standardizing and regulating the protocols and processes of direct-to-consumer genetic tests would be more difficult. Aspects surrounding the nature of performing the test can be regulated (e.g. ensuring the use of calibrated equipment, creation and use of appropriate chemicals, up-to-date instrument maintenance, etc.). However, the choice of SNP variants to include in the test, algorithm to analyze results, and conditions to optimize test performance are much more difficult to standardize and regulate. These variables in testing process would make it difficult to regulate a threshold for false positive and/or false negative rates, too. Finally, if considered a laboratory developed test, the test does not need to be regulated at all. Despite that, however, many laboratories, including 23andMe, are becoming CLIA-certified. Voluntarily becoming and maintaining certification demonstrates a priority of high quality, and can lead to increased trust with the public and any enforcing governmental agencies.

False positive and negative rates vary by lab, test, process, analysis parameters, and genetic region. False positive results occur when the test indicates a positive gene-trait correlation when in fact there is none. False negative results occur when no gene-trait correlation is observed, but there actually is a trait-causing mutation present. False positive and false negative rates are often associated with the accuracy of the test. Therefore, one solution to is to strive towards achieving zero rates for false positive and false negative rates. This is unfeasible, though, because a test cannot eliminate every environmental and human error that can unintentionally, unknowingly, and potentially occur during the process of testing. Scientific tests come with a certain degree of uncertainty and potential for error. Also, in an attempt to eliminate false negatives, one could actually increase the occurrence of false positives. If pushing the limit of detection so low that the test detects every deviation (thus eliminating the potential for a false negative) from the baseline/background, what would normally be in the

background could now be misinterpreted as “clinically significant.” Understanding why errors can occur and respecting that uncertainty is present is important to fully understand results from DTC genetic tests.

Clinical Validity

In order to be considered scientifically robust tests, and therefore suitable for diagnostic use, direct-to-consumer genetic tests must be scientifically and clinically valid. Since a person could potentially make medical decisions based on the results of the DTC test, it is important that he/she receives results that are indicative of his/her true state of health. Finally, tests used for diagnostic or prognostic reasons must be clinically valid; demonstrating a strong correlation between a genetic variant and a certain health condition (Hudson et al., 2007). The newborn screening test and clinical tests for a specific symptom are examples of clinically valid tests. Whole genome screening can be clinically valid if one of the identified gene variants or chromosomal duplications or deletions, for example, is associated with a particular observable manifestation.

Many of the disorders that are tested for in direct-to-consumer genetic tests are of relatively low penetrance (Caulfield and McGuire, 2012). This means that there is a low correlation between a genotype (i.e. DNA sequence) and associated attributes (Caulfield and McGuire, 2012). Utilizing family history and other information, though, genetic counsellors and other medical professionals can use more targeted and valid tests. Second, the usefulness of the information obtained from DTC services is still mostly unproven (Caulfield and McGuire, 2012). There may be a lot of anecdotal evidence, but literature and basic research are lacking.

A final concern with regards to the validity of direct-to-consumer genetic tests is the occurrence of false positive and false negative results. False positive results can lead to more, sometimes invasive tests that result in negative findings. They could also increase anxiety in a person, lead a healthy person to unnecessary testing, intervention, and/or treatment, and ultimately result in wasted healthcare expenses (Edelman and Eng, 2009). Not only can false positive results affect the individual involved, but it can also affect the emotional wellbeing and medical treatment of relatives, given the genetic nature of the DTC testing (Edelman and Eng, 2009). Mammogram testing used in early screening for breast cancer is often criticized for a high false positive rate, or for beginning a painful intervention too early.

False negative results can lead a person to have a false sense of security because they may not be aware that they are still at increased risk of disease (Edelman and Eng, 2009). When symptoms of the disease manifest later, the person and his/her physician could be treating the wrong disease because the actual disease is discounted due to the false negative DTC genetic test result. Receiving a false negative result can be analogous to not taking the test at all, which brings the issue of health equity and access to light. This is an important argument, but is beyond the scope of this paper.

Interpretations and Results

In their 2008 opinion, the American Congress of Obstetricians and Gynecologist (ACOG) included results interpretation difficulty as a key concern surrounding DTC genetic tests (ACOG, 2008). Humans are complex, and so are their genetics. There are tests for some straightforward genetic diseases, as their mutation in one gene can lead to one disorder. An example of this type of disease sickle cell anemia (a mutation in the HbS gene) (Trent, 2014). Not only do genetics

have a part in determining an individual's health, but so do environmental factors.

Environmental factors can play on existing genetics to enhance or decrease the expression of a genetic condition or disease. For example, habitually smoking cigarettes has been shown to act at the DNA level causing lung cancer. A mutation in the well-known BRCA1 and/or BRCA2 genes significantly increase the risk for developing breast cancer, compared to someone without a mutation. However, many types of mutations can influence the risk of an individual contracting breast cancer (Trent, 2014). Given the more complex interpretation necessary for this test, a professional with "considerable expertise" is recommended to analyze the results (Trent, 2014). "Considerable expertise" can include specific education and training in the transmission of genetics and inheritance. Professionals with this level of expertise include genetic counsellors and clinical geneticists. For example, genetic counsellors receive post-baccalaureate education and licensure before practicing in a clinical setting. The additional and specific training allows them to combine family histories, clinical symptoms, and other test results to comprehensively discuss the disorder a person or family may be experiencing as well as the probability of passing it on to their next generation. Clearly, this form of DTC genetic test will be more difficult for an individual to understand without medical professional or genetic counsellor insight.

One of the most complex and difficult to interpret results based on DTC genetic tests is that of Type II diabetes. The testing relies on SNPs, and the risk assignment is derived from an individual comparison to population group (Trent, 2014). Given the many genes and environmental factors involved in Type II diabetes, the testing cannot be considered clinically valid (Trent, 2014). Therefore, even with a reported measured risk, there is very limited meaning to the consumer (Trent, 2014). On the other hand, having a mutated gene may not

manifest as a disorder or disease. Often, the average person has a false assumption of this type of genetic determinism⁴ (Liu and Pearson, 2008). Interviewed professionals agree that the average person has a very basic knowledge of how genetics and the environment combine to influence health. It was noted that an individual may have an understanding of how genetics is related to certain diseases and that environmental factors is related to others, but not how their interaction between them contribute to most diseases.

All of this ambiguity has the potential to lead to unnecessary visits and/or inappropriate follow-up tests in a clinical setting (Caulfield and McGuire, 2012). A 2010 study, showed that 78% of respondents stated they would ask a physician for help with interpreting results (n=1087, Internet survey (Caulfield et al., 2010)). Further, 61% thought physicians have a professional obligation to provide that insight (Caulfield and McGuire, 2012). Even if an individual's physician is not very knowledgeable about genetic testing, in general, the discussion is still valuable to consumers contemplating DTC genetic testing. By consulting with medical professionals before and after taking the DTC test, consumers would be more able to protect themselves and make more well-informed decisions (Liu and Pearson, 2008). Genetic counsellors are well-equipped, through advanced education (i.e. Masters of Science in Genetic Counselling), and trained to educate an individual about risk interpretation and comprehension (Weaver and Pollin, 2012).

It is important to recognize the limitations of surveys, though. For example, simply stating that an individual will do something does not necessarily translate into action (Caulfield and McGuire, 2012). When a survey of DTC test users was performed, only 10.4% discussed

⁴ Genetic determinism - The belief that future health status is determined entirely by genetic makeup (Liu and Pearson, 2008)

results with a company-employed genetic counselor and 26.5% shared results with physician (Caulfield and McGuire, 2012). A physician may realize his/her own lack of knowledge, but consumers may be unaware of their own ignorance of genetics and, therefore, unlikely to seek out more information (Liu and Pearson, 2008). In fact, overconfidence can be prevalent among consumers leading to purchasing tests for the wrong reasons (Liu and Pearson, 2008). The average reading skill level of a U.S. adult is grade 8-9 (middle school), but the reading grade level required to understand much of this complex genetic information is a grade 15 (junior year of college) education (McBride et. al, 2010). Therefore, only approximately 12% of U.S. adults have the necessary health literacy skills required to understand this type of health information (McBride et. al, 2010). This signifies a large gap in the level of understanding necessary to make well-informed decisions and the level of knowledge of consumers making the decisions. Misunderstandings have the potential to lead to increased health care costs by making unnecessary clinic visits, performing unnecessary follow-up tests or procedures, and/or emergency care because of incorrect negative (i.e. no gene-trait correlation) result(s).

To address the anxiety and psychological health concern, the Scripps Genomic Health Initiative occurred in 2009 (Green and Farahany, 2014). It tested 3000 individuals from health and technology companies through Navigenics (who is no longer offering consumer testing) (Green and Farahany, 2014). They performed surveys of the individuals before testing, three and twelve months after (Green and Farahany, 2014). At the end of the study, data from 2000 of the participants were able to be used for conclusions. The initiative concluded that these 2000 participants showed no measurable changes in anxiety or psychological health (Green and Farahany, 2014). Like much else surrounding the after effects of DTC genetic testing, there is little data or evidence to accurately assess the emotional ramifications. Even though concerns of

anxiety, an inappropriate behavioral response, or false sense of security are prevalent, the few studies that have been performed indicated that people generally adapted well to the information provided (Caulfield and McGuire, 2012). However, if the tests are not considered 100% accurate, reliable, or valid, can survey results following DTC tests be considered completely valid either? It should be considered that it may not be reasonable to compare the opinions and reactions of a person's experience to a DTC test if the test, itself, is not accurate, reliable, or valid. The consumer's true viewpoint may not be being expressed as it would be with a valid test.

Concerns surrounding the interpretation of DTC genetic test results arise from the professional performing the interpretation and how those results are communicated to the consumer/patient. Genetic counsellors may be the most appropriate professionals to interpret DTC genetic results because they have specialized training in and a deeper understanding of genetic principles as well as specific board certification in genetic counselling. General practice physicians may not understand the complexities of genetics and predicting to be able to discuss them with patients, or answer questions surrounding the interpretation of DTC results (Caulfield and McGuire, 2012). Furthermore, they may be surprised or blindsided if a patient arrives at their clinic, results in hand, demanding an explanation, and the physician has had no time to prepare.

Interpretations surrounding the accuracy and representativeness of the results is also a concern. First, extrapolating population level data back down to the individual can be inaccurate if that individual does not share other genetic attributes with that population. Complex diseases that involve genetic and environmental factors make it difficult to tease apart the many variables that could be contributing to that disease. If the individual is not showing any symptoms of

disease, that makes the interpretation even more difficult. Finally, interpreting results for incurable diseases is a concern because the results may report a positive or negative result, but will not provide any other meaningful information pertaining to the prevention or treatment of the disease. Therefore, genetic counsellors and clinical geneticists should be consulted to help patients/consumers understand these complex interpretations.

Complex, untreatable genetic diseases, like Huntington's or Alzheimer's disease, carry the greatest amount of risk due to their complexity, neurodegenerative nature, and variation in the population. Alzheimer's disease is a late onset, neurodegenerative, incurable, and fatal disease (Messner, 2011). Its etiology is quite complex because it involves social factors like education, environmental factors like prior head trauma and lifestyle habits, genetic factors like mutation(s) in the APOE gene, and the natural aging process (Messner, 2011). Each factor has an impact on the disease but not an independent, direct link. Data from APOE research can be used to make statistical predictions in populations, but is more difficult at the individual level (Messner, 2011). Messner (2011) conducted two case studies with individuals with very different backgrounds and outlook on genetic testing (Figure 2). The first case was a female journalist with a family history of Alzheimer's diseases (Messner, 2011). She decided to get tested so that she could better prepare for her own future (Messner, 2011). The second case was a male with biology education who took a test offered by his employer to examine his susceptibility to Type II diabetes (Messner, 2011). One case can be considered a positive experience, and the other a very negative experience (Messner, 2011). Both individuals were found to have a genotype predisposing them to Alzheimer's disease (Messner, 2011). Each was shocked to learn the results and received no genetic counselling and little help in interpreting the results (Messner, 2011). In fact, the male individual was simply told to have a healthy diet and

exercise (Messner, 2011). Even though she had a lower risk than she thought, the female individual began taking 50 supplements purported to promote health and cognition as well as make suicide preparations (Messner, 2011). On the other hand, the male individual felt very harmed and angry with the process, and began seeing a psychologist (Messner, 2011).

While these cases are not enough to provide conclusive evidence for policy surrounding results interpretation, they exemplify two ends of the spectrum. The female individual had a clear purpose for performing the test, and although she was surprised by the results, she was able to emotionally prepare. Her positive experience gave her the feeling of empowerment to make proactive lifestyle choices. The male individual also had a clear purpose for performing the test, but he was unaware of the Alzheimer's disease test in addition to examining the predisposition to diabetes. His surprise was due to the inability to be emotionally prepared for his results. Since that knowledge was permanent, his anger was due to the harm he felt from receiving the results without proper counselling.

Figure 2. Side by side comparison of Messner's (2011) case studies

| Female Individual | Male Individual |
|--|---|
| <ul style="list-style-type: none"> - Maternal family history - Limited biology education (journalist) - Refused testing by 5 physicians because asymptomatic - Results same as mother's - Report contained language for a physician and stated that it was not useful for predictive purposes in asymptomatic individuals - No genetic counselling or help with interpretation - Began taking 50 supplements to help with health and cognition; suicide preparations - Believed knowledge is power, and would get tested again | <ul style="list-style-type: none"> - No known family history - Biology education - Employer initiated study of effect of genetic susceptibility testing on health behavior - Curious about predisposition to Type II diabetes - No predisposition to Type II diabetes, but predisposition to Alzheimer's - Genetic counselor advised to eat healthy and exercise - Frustrated with inconsistent results and sought psychologist - Felt harmed and not helped, angry |

Privacy

Genetic information is the most identifying information a person can possess. It cannot be changed the way credit or social security cards can be changed when a person's identity is stolen. Therefore, another concern, primarily for consumers, is the transfer of their genetic information. Consumers may want to keep their DTC genetic results out of their medical record, but disclosing it to and discussing it with their medical professional could lead to that information becoming a part of their medical record after all (Hudson et. al, 2007).

While some claim that they have the right to know their own genetic code (Yim and Chung, 2014), most do not realize that private companies are not necessarily subject to Health

Insurance Portability and Accountability Act (HIPAA) requirements that protect an individual's medical and health information. (Hudson et. al, 2007). Individuals may assume that the same rules of confidentiality with the physician-patient relationship also apply to DTC companies, creating a false sense of security of the protection of their genetic data (Caulfield and McGuire, 2012). There is also the misconception that the public views DTC tests as health information, therefore private (Caulfield and McGuire, 2012). There are no uniform standards for the collection and storage of samples and personal information for DTC companies (Caulfield and McGuire, 2012). This means that data can be used for outside research to a third party or for databasing (Edelman and Eng, 2009). Even if the information is de-identified, aggregated summary or genotype data can still be traced back and identified (Edelman and Eng, 2009). While the benefit of third-party research and databasing is the increased understanding and discovery of genetic diseases, as well as improved tests and testing process, consumers should still have the choice, presented up-front, to participate or not.

In 2008, the Genetic Information Nondiscrimination Act (GINA) was passed (GINA, 2010). This federal legislation protects individuals against discrimination by health insurers and employers on the basis of genetic information (GINA, 2010). However, the act does not require insurance to pay for genetic tests, nor does it prevent them from adjusting rates based on later symptoms and formal diagnosis of the genetic disorder (GINA, 2010). Furthermore, the act is limited to health insurance and does not apply to other types of insurance like life, disability, or long-term care (GINA, 2010). While GINA provides a foundation for consumer rights against discrimination for their genetic predisposition, it does not adequately protect consumers once they begin to show symptoms. These potentially unknown or misunderstood aspects of GINA

demonstrate possible implications for consumers wishing to have their DNA analyzed by a DTC genetic test company.

Ethics

The Hippocratic Oath, “first, do no harm,” resonates when considering direct-to-consumer genetic tests. While it may be inappropriate for the government to mitigate these types of risks, they must still be considered in a comprehensive policy alternative. The potential for consumers to make irrevocable decisions, like terminating a pregnancy, forgoing needed treatments, or pursuing unproven therapies based on their DTC test results is a definite concern (Hudson et. al, 2007). This can be especially disconcerting when the reported results indicate a terminal or untreatable disease. Another ethical concern is testing children for their genetic predisposition or athletic ability traits (Caulfield and McGuire, 2012).

Not only do people have the right to know, but they also have the right not to know. The right not to know is an important distinction with DTC testing because the test can include a specific disease for which a person may not want to know the result. Therefore, an opt-in approach would be a good method to ensure a consumer is obtaining results only for the disease he/she is interested in. Since a company’s primary motive is to collect profits, it introduces a sense of skepticism surrounding the objectivity and scientific validity of their DTC products (Liu and Pearson, 2008).

Other DTC customer attributes included being proficient at utilizing the Internet by seeking other health information online, having a high interest in genetics, and a motivation to change personal health behaviors (McBride et. al, 2010). The Scripps Genomic Health Initiative

also found that each survey suggested that early customers of genomics services were wealthier and more highly educated than the general population, and were more likely to be white (Green and Farahany, 2014). Again, the issue of health equity arises. Paul et al. (2014) asserted that genetic information is becoming more regarded as an exceptional asset. Therefore, knowing more information that can help understand, plan, and control the biological future of an individual's life will give a competitive edge for social and economic resources (Paul et. al, 2014). Will affluent people be the only ones able to afford DTC testing, and will that give them an unfair advantage in health and society? These types of questions are similar to those of other emerging technologies and should be considered with implementation of regulations, but go beyond the scope of this paper. It is possible that the scarcity in health care systems caused the shift in predictive genetic testing from a public health focus to utilizing private health organizations for the information (Paul et. al, 2014). However, with universal health care becoming more common, this part of the health equity issue could become less of a concern.

V. Regulatory action

Federal Regulatory Bodies

The Center for Medicare and Medicaid Services (CMS) regulates all laboratory testing through the Clinical Laboratories Improvement Amendments of 1988 (CLIA) (CMS, 2016). The CLIA program is implemented by the Center for Medicaid and State Operations, Survey and Certification Group, and the Division of Laboratory Services within the Center for Medicare and Medicaid Services (CMS, 2016). The CMS agency establishes federal quality standards for laboratories across the United States that test human specimens for health assessment reasons or

to diagnose, prevent, or treat disease (CDC, 2015). CLIA certification is issued by the Secretary of Health and Human Services, acting through the Public Health Service (Congress, 1988). Any changes to CLIA must go through the rulemaking process including rule proposal, public comment and rule finalization (Serrano, 2016). At least 251,000 laboratories incorporate CLIA in their practices (CMS, 2016). Since 2003, the United States Food and Drug Administration (FDA) has the authority to oversee the CLIA categorization process of determining whether a test should be moderate complexity, high complexity, or waived (Serrano, 2016). The CLIA amendments focus primarily on research and clinical laboratory science, so direct-to-consumer genetic tests are not directly addressed (CMS, 2016). However, an amendment was made in 1997, stating that home use tests could be waived from CLIA if certain guidelines were met (Congress, 1997). These guidelines include being an approved test by the FDA for home use, and determined by the Secretary of Health and Human Services to be “simple” and to pose no harm to the patient (Congress, 1997) (neither attribute applies to DTC genetic tests). Finally, the Centers for Disease Control (CDC) also has a small role with direct-to-consumer genetic tests, too. Their role is more behind the scenes, but important nonetheless. The CDC is responsible for providing technical assistance, developing standards and laboratory practice guidelines, and manages the Clinical Laboratory Improvement Advisory Council (U.S. FDA, 2015). In terms of direct-to-consumer genetic testing, the CDC is involved in the broader, laboratory practices instead of the tests themselves. Although, they could become more involved if scientists at a CLIA-certified laboratory/company undergo regular proficiency testing that is monitored by the CDC (U.S. FDA, 2015).

The United States Food and Drug Administration (FDA) has become the primary regulatory authority for direct-to-consumer genetic tests because they categorize health related

tests. Since 1976, the FDA has had jurisdiction over in vitro diagnostic devices, without distinguishing between laboratory developed tests or direct-to-consumer tests (Serrano, 2016). The FDA regulates devices, intended to be used for diagnostic, cure, mitigation, treatment, or prevention of disease purposes under the Federal Food, Drug, and Cosmetic Act (CMS, 2013). One of the challenges with direct-to-consumer genetic tests is that they fall between the FDA definitions of laboratory developed test (LDT) and medical device. Laboratory developed tests are diagnostic tests that are designed, manufactured, and used inside one laboratory (U.S. FDA, 2015). According to the FDA website, a medical device is “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article...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. FDA, 2015). Under the FDA’s “enforcement jurisdiction,” the agency can choose whether or not to enforce laws or regulations on devices (Serrano, 2016). Additionally, the high risks and benefits in a situation where a test is ordered and received directly by a consumer exemplifies why the FDA addresses DTC genetic tests individually and not using an enforcement discretion based policy (Serrano, 2016). One could argue that since DTC tests are developed, manufactured, and tested within a single laboratory, they should be classified as an LDT. However, it could also be argued that these types of tests unofficially (i.e. without a physician) diagnose a disease or the results aid in the mitigation or treatment of a disease. In fact, the FDA issued a warning letter to DTC company 23andMe in 2013 for failure to obtain FDA approval for DTC tests that were deemed to fall under the definition of a medical device (U.S. FDA, 2015). A test kit for diagnostic purposes requires premarket approval to review its analytical validity, labeling, and adverse-event reporting after the test kit is released to the market (Hudson et. al, 2007).

Laboratory-developed tests, on the other hand, do not require premarket approval or reporting of adverse events after the test was released (Hudson et. al, 2007). The FDA has not, generally, enforced the premarket review process for LDTs because they were simple laboratory tests that were available on a limited basis (U.S. FDA, 2015). But with advances in technology, LDTs have evolved and expanded to be more complex, have a further reach to consumers, and present higher risks (U.S. FDA, 2015). Thus, DTC tests are increasingly blurring the line between LDT and a medical device.

Product-centered regulation could be used for direct-to-consumer testing based on the risk level of the genetic test. Risk level can be assessed utilizing a two-term classification scheme. The first term describing whether the disease is due to one gene (simple) or more than one gene plus environmental factors (complex). The second part of the term could describe whether the genetic disease is treatable or untreatable. For example, DTC tests that test for untreatable, complex diseases, like Alzheimer’s disease, would have a different set of guidelines than untreatable, simple diseases (e.g. Huntington’s disease), treatable and complex (e.g. Type II diabetes), or treatable and simple (e.g. phenylketonuria) diseases (Figure 3). The challenge would be keeping pace with the advances of genetic discovery to ensure that new treatments and diseases were accurately placed in the appropriate set of guidelines.

Figure 3. Two-term classification scheme for evaluating risk level of a DTC test, and examples.

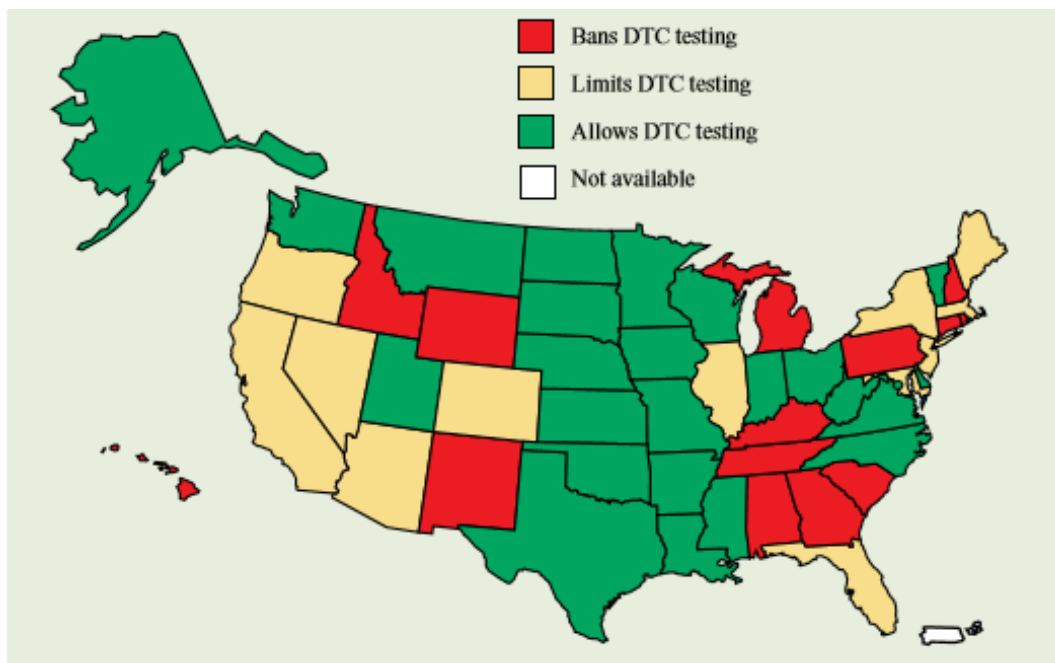
| | Simple (one gene) | Complex (one or more genes + environment) |
|--------------------|--------------------------|--|
| Treatable | Phenylketonuria | Type II diabetes |
| Untreatable | Huntington’s disease | Alzheimer’s disease |

Another federal agency with influence over direct-to-consumer genetic tests is the Federal Trade Commission (FTC). The FTC is responsible for consumer protection, including protecting against deceptive advertising (FTC, 2016). Deceptive advertising was previously found in DTC genetic testing companies (FTC, 2016). A major limitation in the FTC's ability to take action is the fact that the government has limited ability to restrict commercial speech (Hudson et. al, 2007). Within the context of DTC genetic tests, it is difficult to regulate company claims since so much is still unknown of the nuances and fine details of genetic diseases. If a DTC company is not being overtly inaccurate or fraudulent in their claims, but may be overstating the power of their tests, then it is possible that the company is not committing deceptive advertising by FTC standards. In 2006, though, the agency issued a consumer alert warning the public that some DTC tests lacked scientific validity and that others provided meaningless medical results unless they were taken in context with a full medical evaluation (Hudson et. al, 2007). The alert asserted that consumers should interpret DTC genetic tests with a "healthy dose of skepticism" and to "be wary of claims about the benefits these products supposedly offer" (Caulfield and McGuire, 2012). Aside from these warnings, the FTC has not taken any direct action against DTC companies (Hudson et. al, 2007). Both the FTC and CDC also advise discussing the testing with a physician or genetic counsellor before and after testing to ensure that the consumer/patient has a full understanding of what the test offers and what the results mean (ACOG, 2008).

Over half of the states in the US allow some form of direct-to-consumer genetic testing, though in some the test must be done through a provider (Hudson et. al, 2007) (Figure 4). Laws vary from state to state because each state's definition of the practice of medicine can be different (Caulfield and McGuire, 2012). If a state defines medical practice as referring to the

diagnosis and/or treatment of a disease, condition, or injury (Caulfield and McGuire, 2012), then DTC tests could fall under that definition. Furthermore, consumers that purchase and utilize DTC testing usually believe test results to be the same as health information or a medical diagnosis (Caulfield and McGuire, 2012). Therefore, if tests sold with the consumer believing that the test is, or at least complements, a medical diagnosis, the test should be regulated more stringently.

Figure 4. Map of the United States showing which states allow, limit, or ban direct-to-consumer genetic testing (Goodwin, 2008).



The state of Minnesota has several statutes surrounding genetic testing and genetic information, in general. For example, statute 144.1255 calls for the creation of an advisory committee to discuss genetic testing, treatments, and other issues pertaining to heritable and congenital disorders (Office of the Revisor, 2015). Another statute, 144.192, addresses the collection,

storage, and use of genetic information (Office of the Revisor, 2015). Finally, statute 181.973 determined that genetic information as protected information, and must be treated as such in employment situations (Office of the Revisor, 2015). A review was conducted in 2009 comparing Minnesota law to GINA but there is not a state statute directly addressing direct-to-consumer genetic testing.

Globally, the political environment is somewhat different than the United States. For example, Germany has banned DTC testing, and the Australian Medical Association supports a ban primarily due to the concern about misinterpretation of results (Caulfield and McGuire, 2012). The United Kingdom Human Genetic Commission and European Society of Human Genetics have a similar approach to some US states in that they support DTC testing but with appropriate genetic counselling (Caulfield and McGuire, 2012).

Government Accountability Office (GAO) investigation – 2006 and 2010

A lot of development surrounding direct-to-consumer genetic testing has occurred within the last fifteen years, but it was not until 2006 that governmental agencies began to examine DTC companies and consider implementing more stringent oversight. In 2006, the Government Accountability Office (GAO) initiated an investigation, based on misleading claims, of some of the DTC companies that offered genetic testing combined with the sale of nutrigenetic advice and supplements (Caulfield and McGuire, 2012). The GAO purchased tests from four companies⁵, two of which also sold expensive dietary products, and one of which was not accredited (Trent, 2012). The companies also had disclaimers stating that the genetic tests were

⁵ Companies were not named in the GAO final report (U.S. GAO, 2010).

not intended to diagnose disease, even though results reported risk assessments for diseases (Trent, 2012). Using real DNA but false personal information, the GAO submitted samples comprising fourteen false personas. Upon obtaining results, the GAO reported that the companies misled consumers by making medically unproven and ambiguous predictions that did not provide any meaningful information (Caulfield and McGuire, 2012). Further, despite the disclaimers that the tests were not for diagnostic use, the reports on all fourteen (false) individuals identified them as being at risk of contracting osteoporosis, cancer, Type II diabetes, hypertension, and other conditions (Trent, 2012). Finally, the GAO noticed that the data was inconsistent, even when the same DNA sample was used for two different “individuals” (Trent, 2012). Though the sample size was small, the GAO investigation highlighted inconsistencies in practices and results.

The GAO conducted a follow-up study and expanded investigation in 2010, including the companies 23andMe, Navigenics, and Pathway Genomics (Trent, 2012). Again, the GAO found their results to be misleading and of little to no practical use (Caulfield and McGuire, 2012). Additionally, because they were investigated in 2006, the four labs were examined again in 2010, and the GAO found that little improved (Trent, 2012). Of the fifteen companies audited in 2010, the GAO reported that ten of them engaged in some form of deceptive, fraudulent, or otherwise questionable marketing practices (Trent, 2014). They also reported that even though each company claimed that their product was grounded in the most recent and best science, results showed a large amount of variance from the different companies (Caulfield and McGuire, 2012). It was found that the inconsistent results could be due to the fact that each company employs different panels of specific SNPs to analyze and use different algorithms (Trent, 2012). Also, applying population-based studies to the results of an individual person could cause

inconsistencies because individuals and their traits comprise the population, not vice-versa. GAO's investigations and findings exposed inconsistencies that were being experienced by consumers and laid the groundwork for future possible policy and identified areas where companies could improve to become more competitive in the DTC market.

23andMe – 2013

The most well-known case regarding direct-to-consumer genetic testing is the story surrounding DTC company 23andMe. This company offered personal genome services to more than 475,000 customers between 2007 and 2014 (Yim and Chung, 2014). 23andMe advertised to have created a customized SNP-chip to provide reports on, originally, 254 genetic diseases and traits, including responses to drugs and carrier status (Yim and Chung, 2014). It was discovered that 23andMe was not performing the testing in-house, which is required by the FDA for the test to be considered a laboratory developed test. Instead the samples were being sent to another lab for testing (Trent, 2014).

In 2013, the FDA intervened and issued a warning letter, directing 23andMe to cease its sale of Personal Genome Services because they failed to obtain clearance for marketing or FDA approval to assure that the tests were accurate, reliable, and clinically meaningful (U.S. FDA, 2015). The FDA argued that pre-market approval was required because the tests were intended to be used “in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or is intended to affect the structure or function of the body” (U.S. FDA, 2015). In other words, the FDA concluded that the tests should be classified as medical devices (which requires premarket approval) (U.S. FDA, 2015). Supporters of the FDA's action argued

that it protected consumers from possibly inaccurate information, while opponents countered that the action was a violation of individuals' right to information, damaging the democratization of health care and patient empowerment (Yim and Chung, 2014). Despite the block against the sale of DTC tests, 23andMe continued to sell the tests in Canada well into 2014 (Yim and Chung, 2014). After working with the FDA, 23andMe had their Bloom Syndrome carrier test⁶ authorized as a Class II device on February 19, 2015 which is exempt from premarket review (U.S. FDA, 2015). Medical device classification is determined by the intended use of the device, the indications for use, and the risk level (U.S. FDA, 2014). Class I devices have the lowest risk, and Class III devices have the highest risk (U.S. FDA, 2014). Therefore, Class II devices have a moderate level of risk to the consumer. The FDA also required that results of the carrier test, including labeling, be conveyed in a manner that consumers would understand and use (U.S. FDA, 2015). Today, 23andMe sells one kit that includes more than 60 genetic test reports including carrier status for cystic fibrosis and sickle cell anemia, reports of ancestry, wellness reports for caffeine consumption, and traits reports for hair color and facial features, among many others (23andMe, 2016). They do not carry tests for complex or untreatable diseases like heart disease, Type II diabetes, Alzheimer's, or Huntington's disease (23andMe, 2016).

VI. Attributes of an effective policy and policy alternatives

The consequences due incomplete and inconsistent regulation could lead to a decrease in public trust and negative impacts on new and conventional DNA genetic testing and research

⁶ Carrier testing is intended for adults and prospective parents with a family history of a genetic disorder. It can be performed on those who display no symptoms for a genetic disorder, and therefore, are at risk for passing it on to their children. The testing should be used in conjunction with other information, and with the assistance of a genetic counselor or other medical professional. (U.S. FDA, 2015)

(Trent, 2012). Interviews of a genetic counsellor for the University of Minnesota, a HealthEast pediatric clinician, and an FDA regulatory official in biology were conducted to gain insight from those working more directly with genetic testing. Their familiarity with direct-to-consumer genetic tests spanned from very familiar to somewhat familiar. When asked if they would support DTC genetic testing, given their background, experience, and profession, responses were “yes,” “no,” and that the decision is a “personal choice.” Supporting DTC genetic testing was important for families that are at higher risk or have a family history of a genetic disease (e.g. β -thalassemia, sickle cell anemia). Not supporting DTC genetic testing was due to the fact that much of the application of the testing was not proven to be tied to the genetic disorder(s). The respondents noted that examining family history, and using a targeted test was a much more accurate way to perform genetic testing. Given the amount of discussion necessary with these professionals, genetic testing should be performed in a clinical setting and not direct-to-consumer. Finally, all respondents agreed that an individual desiring to perform a DTC genetic test should be able to retrieve information related to their own health.

In a 2013 survey, 84% of the 1,046 eligible respondents stated that oversight, in general, by a non-governmental group (e.g. the Better Business Bureau) was very or somewhat important in regards to direct-to-consumer genetic tests (Bollinger et. al, 2013). But, the survey also found that 66% of respondents believed that it was very or somewhat important that DTC testing services should still be provided without governmental oversight (Bollinger et. al, 2013). Interestingly, the survey also found that those respondents that had low levels of satisfaction with the value of the DTC results were more positive toward regulation (Bollinger et. al, 2013). The take-away message from this survey is that people are generally favorable of some type of

oversight, but argue that direct-to-consumer genetic tests should still be available regardless of the level of oversight.

Direct-to-consumer genetic testing policy will need to be flexible enough to account for the wide array of genetic diseases. DTC policy must also be adaptable because of the fast pace of innovation and discovery occurring in the field of genetics and biotechnology. Hard regulations would be difficult to effectively enforce, and could stifle technological innovation. Relying too much on guidelines would be too soft of an approach, essentially leaving regulations to the DTC companies to be on the honor system. Applying a product-by-product approach to DTC genetic testing policy could be one method. Therefore, a blend and balance of the two policy approaches examining each product as it is developed would be the most effective.

Interventions at each of the four types of risks discussed below (company claims/marketing, clinical validity, testing process, and interpretations and results) could be another way to regulate direct-to-consumer genetic testing.

1. Company Claims/Marketing

Simple transparency regarding the limitations and extent of the direct-to-consumer test would increase the company's integrity and trust with its consumers. Companies could also introduce an ala-carte menu of genetic tests for consumers to opt-in to the specific test they want performed on their DNA. Regulatory intervention at this level is unlikely, though, due to the right of commercial speech for private companies. Continuing their collaboration, the FDA and FTC could mandate that DTC companies specify the harms and limitations of the test(s), discuss the probabilities surrounding genetics, and list attributes related to the tests' accuracy and utility

(Liu and Pearson, 2008). Finally, enforcement action would be delegated to the Federal Trade Commission (FTC), and limited to ensuring that nothing misleading or fraudulent was being communicated to consumers.

2. *Testing Process*

Adding regulations or guidelines to aspects of the testing process would be the most straight-forward action. Machinery and protocols are easier to standardize and make more consistent. Aspects such as employee qualifications and laboratory practices can be standardized across companies, too. Applying the Clinical Laboratory Improvement Amendments (CLIA) to aspects of direct-to-consumer testing laboratories would aid in this standardization. The Centers for Medicare and Medicaid Services (CMS) could introduce new regulation that all DTC companies must be CLIA-certified. Since Food and Drug Administration (FDA) already enforces standards described in the CLIA, an additional regulatory agency to investigate the testing process of direct-to-consumer tests is unnecessary. For example, 23andMe is CLIA-certified, demonstrating that the company holds its testing process and employees to a higher standard than a company that is not CLIA-certified. This would create an upfront cost to ensure that the laboratory meets all criteria to be CLIA-certified, as well as any ongoing costs to maintain certification. However, obtaining and maintaining CLIA certification would demonstrate that the company is serious about the quality of its tests and its concern for consumers.

In addition to, or in place of, certification, professional organizations could issue best practice guidelines in the interest of maintaining consistency and high quality work from their members. These guidelines would be developed as an example of how best to process, interpret,

and communicate results to patients/consumers. Guidelines could include appropriate quality control measures to minimize the amount of error in the testing process, like laboratory space set-up, contamination minimization, and work practices to avoid sources of error. Guidelines could also include recommended parameters or settings for the testing platform or analysis algorithms. These guidelines would make companies who chose to participate more consistent with each other. However, as with many professional organizations, the membership would be voluntary. Furthermore, companies may be resistant because it is a significant measure where they could use different guidelines to be more unique or competitive with a rival company.

An intervention could take place prior to the laboratory testing, too, when the patient/consumer is in the clinic, discussing the possibility of direct-to-consumer genetic testing with his/her genetic counsellor or physician. While conducting a pre-test consultation would be the most efficient way to undergo the DTC process, enforcing this requirement would be difficult due to the potential lack of availability of clinicians or genetic counsellors, refusal of insurance companies to cover the cost, or disinterest from the consumer. When asked about what elements the interviewees felt should be included in a conversation with an individual interested in DTC genetic testing, there were similar themes across professions. For example, a discussion about the intent, or why the consumer wanted to pursue genetic testing, was important. Second, each interviewee would discuss the limitations of the genetic testing, value, and what the consumer should and should not expect to learn from the test. Third, a discussion about the science behind the testing was stated to be an important component. This would have a cost associated with it, either out of pocket for the consumer or from the insurance company, and could create long wait-times for an appointment at the clinic. However, once each party adjusts to the new system, the benefits of more well-informed consumers would outweigh the cost.

3. Clinical Validity

Ensuring the accuracy and clinical validity of the direct-to-consumer test, could be demonstrated through the use of regulated labeling. The biggest impact this type of policy could have is creating a consistent and level playing field for DTC companies and their consumers. As an example, the FDA could work with the FTC to develop required language for disclaimers and/or other claims made by the DTC company (e.g. written in plain language). Interagency collaboration and coordination is important to minimize gaps in DTC genetic testing policy. Additionally, the FDA and FTC could mandate or pressure DTC genetic test companies to change their packaging and other marketing practices to ensure that consumers can make a more well-informed choice (Messner, 2011). Mandates for disclosure of information would be in the form of formal regulations. Pressure for disclosure of information would more similar to soft law measures, like guidelines or access to specific databases. Increasing the amount of regulations too much on the way companies do business, as far as approval steps, labeling, etc., could create a high barrier to entry into the market, or make the process too expensive for DTC companies.

4. Interpretation of Results

Protection of the consumer/patient is of utmost importance when considering regulation of direct-to-consumer genetic tests. True, consumers have a right to the most private information of their own body, but they should be able to collect and store that information without it being exploited by DTC companies. With so many options for testing for genetic diseases of varied severities, it is clear that a “one-size-fits-all” approach is not appropriate for DTC tests (Hudson

et. al, 2007). Therefore, a tiered approach based on the genetic disease should be considered. For example, simple, treatable genetic diseases (e.g. PKU and Cystic fibrosis) could be performed by DTC with a small amount of counselling following to set-up a treatment plan. Complex, treatable diseases (e.g. heart disease and Type II diabetes) would require considerably more counselling and follow-up due to the more complicated nature of the genetic disorder. Primary physicians and genetic counsellors would need to be involved so the patient receives the most comprehensive care. Simple, untreatable diseases (e.g. Huntington's) should be done with counselling prior to, during, and after testing. This type of testing can cause severe emotional harm if care is not taken proactively to discuss the nature of the disease, attributes of the test, and an understanding of interpreting and using the results. As a result, this type of test should not be available as a DTC genetic test. Finally, complex, untreatable diseases (e.g. Alzheimer's) should be given the most caution and counselling because there are no clear correlations with the disease. Patients interested in these diseases should be counselled by a genetic counsellor or medical professional prior to, during, and after testing as well. Therefore, testing for these diseases should not be available as DTC genetic tests either.

With the intervention of adding an intermediary (i.e. genetic counsellor or clinical geneticist), the process is no longer 100% DTC. This could increase costs to insurance companies and/or consumers due to the referral process. There is also the risk of misinterpretation by the physician or genetic counsellor, but the patient is at no greater risk than without any interpretation. Though the risk of misinterpretation for clear, unambiguous results is low, the risk for "borderline" positive/negative results would increase or decrease depending on the medical professional's education and experience with DTC tests.

Interview responses regarding policy alternatives

Three questions were posed to interviewees related to policy alternatives:

1. Who should be responsible for ensuring that results are conveyed in an easy to understand format?
2. Should policy surrounding DTC predictive genetic testing be determined by the market or by government regulations?
3. What would be the three most important factors for a policy regulating DTC predictive genetic testing?

Assigning responsibility to a specific entity (company, Congress, consumer, government agency(ies), professional organizations, or researchers) was varied across the interviewees. One felt that the company was ultimately responsible for communicating results because they are the ones marketing the tests. The other two felt that a collaborative approach was more appropriate. For example, consumers should have a right to access their genetic information, and companies should share some of the responsibility in communicating limitations to the consumers. Professional organizations can assist with developing policy, educating physicians, and providing resources to help create a framework from which governmental agencies can perform oversight of the company's claims and communication/interpretation of results. This would allow for effective policy without stifling the DTC company's innovation. Consumers will have some responsibility as well, but it will be challenging due to the low level of genetic understanding found in the public.

Responses to whether the market or governmental regulations should drive policy were somewhat more consistent. The basic consensus was that the market ultimately drives genetic

testing. It was also noted that a combination of forces plays a small part, too, because the government responds to the public's interaction with DTC genetic tests. One interviewee stated that the government should not allocate resources to educate the public at the expense of other policies. Another interviewee commented that mitigating risks to consumers was important as government responds to the market drivers to move forward with DTC genetic testing.

The range of responses for the three most important factors for a policy demonstrates the complexity of regulating DTC predictive genetic testing. Related to the consumer, it was important that education be a main component, including understanding the consumer's level of genetic knowledge in order to mitigate the amount risk. It was also stated that clearly explaining the type, purpose, and limitations of the DTC test and its associated risk were important. Finally, a discussion ensuring that the consumer was aware of the informed consent process was noted to be important. This education piece alone touches on assessing a basal knowledge level, discussing risk, discussing technical information, and addressing privacy concerns. Clearly, an effective policy will have impact in many different aspects of society. At the scientific level, it was noted that it is important to ensure the scientific robustness of the DTC tests and their subsequent results accurately reflect the identity and risk level of a genetic disease(s). The final layer of a policy regulating DTC predictive genetic testing includes a level of company transparency and federal oversight. A level of oversight was important to assign some accountability to the companies, but details pertaining to where and how oversight should occur were not discussed.

Evaluation criteria

Evaluation criteria to determine the most effective policy must be comprehensive, considering the interests and needs of the medical professional, government agency, DTC company, and consumer. First, consumer/patient safety is the top priority. The risk of harm to the consumer/patient must be as low as possible or alternatives to mitigate the risk must exist. This includes physical and emotional harm. Other evaluative criteria include cost, system efficiency, and the effect on biotechnological innovation. Cost is an important factor because the cost of health care is already high. Adding cost to the patient/consumer would make it more difficult for equal access to DTC genetic testing. With universal health care in effect, all citizens must be covered by health insurance, but depending on the company, that coverage may or may not include DTC genetic testing. System efficiency is important for a similar reason as cost. The current health care system is already fairly inefficient, and adding an intervention step to further decrease efficiency would make the utilization of DTC testing less appealing to the consumer. For the more complicated tests (e.g. Alzheimer's, Huntington's, and Type II diabetes), a referral would be necessary as it would require multiple consultations with a medical professional, but only one meeting may be necessary for the simpler test (e.g. PKU). Finally, policy should stifle biotechnological innovation as little as possible. Protecting the consumer and the greater public health is important, but regulations should not be so strict that the companies cannot advance treatment development, genetic discoveries, or promote personalized medicine.

VII. Recommendations

Direct-to-consumer genetic tests is a type of emerging technology that creates an interesting tension between the potential for benefits and uncertain risks for human health. Furthermore, because of the amount of uncertainty surrounding the potential for these technologies, future risks are difficult to accurately predict. Performing a complete overhaul and rebuild of regulations for DTC genetic testing is not feasible. Therefore, this paper provides three recommendations related to CLIA-certification, direct-to-consumer test classification by the FDA, and minimum labeling requirements. These recommendations accomplish goals such as filling gaps in regulation and knowledge, policies that do not stifle innovation, and allow for good stewardship, adaptability, and stakeholder involvement.

Recommendation #1 – CLIA certification

First, this paper makes the recommendation that all direct-to-consumer companies be CLIA-certified, enforced by the FDA. Certification and accreditation is occurring in clinical labs, research labs, and crime labs across the country, so it is reasonable that private DTC companies also become certified. Certification would address the testing concern by establishing a more consistent and standardized testing process. While components of the process may differ slightly, such as the array of SNP variants or analysis algorithms protected by the company's trade secrets, the process itself will be more consistent. Company certification could also decrease the error rate of DTC testing as a whole, and support a competitive level of quality among DTC companies. Though there will be the ability for continued development through

regularly scheduled assessments/audits, obtaining and maintaining the certification will be a cost for companies to absorb.

Indirect effects are related to clinical validity. By mandating a minimum standard but allowing companies to remain competitive, direct-to-consumer tests could become more clinically valid and accurate. Accurate identification of a gene variant and its precise correlation to a clinical syndrome would increase the tests' accuracy and clinical validity. Finally, increased test accuracy could lead to a decreased occurrence of false positive and false negative results. Professional organizations can play a role in developing guidelines so that patients/consumers understand the testing prior to, during, and after performing the test. Medical professional belonging to professional organizations and the DTC company can have an impact with this recommendation by preparing their respective laboratories for the certification process. If needed, they could consult with researchers or other professionals who are CLIA-certified to prepare effectively and efficiently. Medical professionals can also fill a role by educating their patients on the meaning of CLIA-certification when consulting prior to genetic testing. Overall, mandating CLIA-certification will increase the protection of patient safety and efficiency by forming a minimum standard for the industry without halting DTC genetic test innovation with a low, relative cost.

Increased safety and accuracy of direct-to-consumer genetic tests are important ethical implications of this recommendation. It allows for better patient/consumer protection and an increased public trust with the company and technology. However, simply requiring CLIA-certification may not be enough to fully protect the consumer. For example, consumers may not understand what CLIA-certified means or why it is important. This recommendation does not address the marketing aspect of direct-to-consumer genetic tests, so companies still have the

ability to overstate their claims or otherwise mislead the consumer into buying their product. If a laboratory offers more than one genetic test, it may be more appropriate to certify each individual test instead of the laboratory as a whole. Finally, requiring CLIA-certification does not address the results of the test, nor how they are interpreted by the consumer. Therefore, CLIA-certification is a good first step in protecting the consumer from the risk of harm to the lack of or misinformation, but should be implemented in conjunction with the next two recommendations.

Recommendation #2 – FDA classification of DTC tests and corresponding genetic disease

To increase standardization and efficiency, each new genetic test should be evaluated by the FDA to determine which classification of test it best fits (simple/treatable, simple/untreatable, complex/treatable, or complex/untreatable). This recommendation addresses three of the four areas of concern – company claims/marketing, testing process, and interpretations and results. Using the four classifications (simple/treatable, simple/untreatable, complex/treatable, or complex/untreatable disease) will aid in educating the consumer by breaking down complex information to be more understandable to the average person, thus narrowing the knowledge gap. It will also aid in standardization for CLIA-certification and testing processes. Proper classifications will also aid in the development and marketing of DTC genetic tests by creating a common list of terms and definitions. The classification system would indicate to an insurance company the necessary and appropriate referrals and consultations with a medical professional so the consumer/patient is able to receive the necessary education and results understanding required given the complexity of DTC tests.

Other classification systems can be considered or utilized by the FDA in the development of a classification system most appropriated for direct-to-consumer genetic tests. However, other systems are based more on traditional genetics or the transmission of genes. For example, classic genetic classifies genetic diseases as one of three types: single-gene, chromosomal, and multifactorial (Nussbaum et. al, 2004). Single-gene disorders involve one mutated gene (Nussbaum et. al, 2004), similar to this paper’s “simple” classification. Chromosomal disorders involve the excess or deficiency of a piece of or an entire chromosome (Nussbaum et. al, 2004). This paper does not use this designation because an excess or deficiency of a part(s) of a chromosome can involve one gene (simple) or more than one gene (complex). Finally, multifactorial disorders involve multiple variations in genes as well as environmental factors (Nussbaum et. al, 2004), similar to this paper’s “complex” classification. Traditional classifications such as this one do not account for the clinical manifestations or treatment availability. Therefore, this paper’s proposed classification system uses traditional genetic foundations and combines it with clinical manifestations to create a simple framework of terms that can be easily understood by clinicians, geneticists, and consumers. Medical professionals will play a vital role in advising the FDA as to the most appropriate categorization of each genetic disease.

One ethical concern is the determination of who or what agency will be charged with classifying the tests into their respective category. The person or agency charged with this task will need to be knowledgeable enough to understand the clinical and genetic attributes of the disease being tested, organized enough to develop and maintain the classification system, and proactive to keep pace with the tests being developed. It is unclear whether utilizing a classification system will be adequately communicated to the consumer. Furthermore, it is

unclear whether the average consumer would understand such a classification system given the large health knowledge gap. Not only would consumers need to be educated about the classification system, but physicians, genetic counsellors, and other medical professionals will need to be educated as well.

Another ethical concern is how insurance companies could use the classification system against the consumer. It is possible that a person would be labeled without the insurance company having a complete understanding of the needs of the test consumer. Even though GINA protects against insurance enrollment based on a genetic condition, once the person begins to show symptoms of that genetic disease, the insurance company can a person's rates (GINA, 2010). Not only could being labelled traumatically affect a person, but possible future conflict with an insurance agency could be traumatic as well. Emotional trauma could still affect a person by being labelled, even if they purchased the test out-of-pocket.

The biggest challenge for this recommendation will be the cost of maintaining the list or database of known genetic disorders as well as those discovered and developed in the future. Another challenge would be re-classifying a genetic disease, if needed. Regulations that are too rigid in the definitions for the classification scheme will not allow genetic diseases to change categories upon further research. This could lead to inappropriate follow-up care due to misclassification. The FDA must be prepared, as well, for the possibility that a genetic disease may fall in-between categories, and how best to classify it. However, utilizing a classification system could prevent companies from overstating the power of their DTC test, allowing the consumer to make a more well-informed choice.

Recommendation #3 – Consistent and clear labeling practices

Finally, once the FDA classifies the test, consistent labeling should clearly and in plain language describe the disease being tested, the classification, and other pertinent information. Standard labeling practices would address the company claims/marketing and interpretation and results concerns. A label describing the gene-disorder relationship and whether it is a simple/treatable, simple/untreatable, complex/treatable, or complex/untreatable disease will clearly convey the DTC test to the consumer. It will also create a level of transparency which will decrease the knowledge gap between the DTC company and the consumer. Accurate labeling will force companies to address limitations of their DTC test, especially if results are expected to be ambiguous.

Stakeholder involvement could occur at the pre-implementation and education areas of the process. Medical professionals collaborating with the marketing team of the company would result in a more effective label accurately describing the goals and limitations of the test. They could also fill a vital role of educating other medical professionals as well as consumers. A panel of consumers will also provide helpful insight into the efficacy of proposed labeling.

There will be a cost to the company to implement the specific labeling requirements, but the benefits will outweigh the cost in terms of patient safety and efficiency. A long-term cost will be the enforcement of the labeling standard by the FDA or FTC. The ability to compare DTC companies and tests side-by-side will allow for consumers to make a better informed choice. Finally, ensuring that a minimum amount of information is being conveyed to the consumer/patient will create a standard and level of consistency for DTC genetic tests and companies.

Ethical concerns surrounding labeling are similar to that of the classification system recommendation. The first being the determination of who or what agency will determine the contents and presentation of the label. A second concern surrounds the health knowledge gap of the average person. Again, avoiding misleading information from the company's marketing will be important. Finally, it will be important that the consumer understands what the label means so that they can choose the most appropriate test without having the consultation of a physician, genetic counsellor, or other medical professional.

Concerns discussed for all previous recommendations assume that the consumer has access to health insurance. There are many other ethical concerns surrounding the lack of access to health insurance or health inequities. Everyone, not just those affluent or wealthy enough to afford it, should be able to have access to testing that gives them increased knowledge about their current and future health. These concerns must be considered as well to develop comprehensive and effective policy.

VIII. Conclusion

These recommendations introduce some minimal regulations for DTC companies, and keep the consumer's/patient's safety in mind regarding direct-to-consumer genetic testing. Mandating that all DTC companies become CLIA-certified, establishing a classification system for the DTC genetic tests by the FDA, and establishing minimum labeling requirements introduce regulations with minimal cost to the company. Creating and maintaining a balance is important with DTC genetic tests because of the highly sensitive and personal information it reveals. A consumer's right to that information and for them not to be exploited is the basis for

much of the recommendations. However, regulations must not be so protective of the consumers that the government unintentionally prevents consumer access to their personal information.

These recommendations suggest a balance for regulations mandating a minimal level of quality from DTC companies with consumer safety. With that balance, though, consumers must take initiative to become well-informed about the tests they are purchasing, and use that purchasing power to influence the company to create the best possible product. All stakeholders (regulators, consumers, medical professionals, and DTC companies) must work collaboratively to ensure that DTC genetic tests are being utilized efficiently, effectively, and for the purpose of curing and treating genetic diseases.

One the biggest challenges in regulating direct-to-consumer genetic tests is determining a consensus regarding personal and social values, if there is a consensus. Because of the highly sensitive and personal information that can be revealed through DTC genetic tests, the utilization of that information is very subjective. Some people believe that knowledge is power, and a person should find out everything they can about their genetic past, present, and future. Others believe that utilizing genetic information should not be allowed to predict and treat future diseases without symptoms present. Many people, though, are somewhere in the middle. For example, DTC genetic tests should be used for genetic diseases where there is a known gene-trait correlation and treatment but should not be utilized for diseases where there is no treatment. Reasons behind the various viewpoints could involve quality of life, cost of treatment, playing God, and/or fear. Where a person draws the line between acceptable and unacceptable use of DTC genetic tests could also vary from situation to situation. These situations could include child vs. adult, cost of treatment vs. cost of not treating, and fear of discovering a genetic disorder vs. fear of not discovering a genetic disorder until it is too late for treatment, among

others. This delicate and subjective balancing act highlights why regulations must be flexible, adaptable, and avoiding a “one-size-fits-all” approach. It also demonstrates the importance of medical professionals consulting with consumers/patients prior to and after using a DTC genetic test. A proper consultation will help the consumer/patient address concerns and feelings as they determine the most optimal value tradeoffs for their unique situation.

Clearly, direct-to-consumer genetic tests are only at the beginning of their technological and public health potential. Not only will the technology continue to be innovated and expanded, but regulations could also help DTC genetic tests reach their full potential. Interest in DNA technology will continue to strive toward understanding the most foundational building blocks. Therefore, DTC genetic technology innovation will discover more gene, SNP, and other mutational correlations with diseases as well as make their tests more accurately pinpoint the cause of a genetic disease. Eventually, they can be expanded to routine whole genome analysis. Instead of looking at one or a few gene/SNP-trait correlations, a DTC company could sequence a consumer’s entire genome as a basal test or looking for other single nucleotide mutations. Then, later, when the consumer displays symptoms of an unknown ailment, the genome could be sequenced again to search for any new variations in the DNA. Increased distribution of DTC genetic tests could lead to higher use by consumers of various populations. Consumer feedback and input could help the DTC company develop more accurate results, make their tests more effective for consumers, developing new tests, and/or make existing tests more effective.

One of the most positive outcomes from these recommendations is the increased consistency and standardization across direct-to-consumer genetic tests. Tests produced by the company will also be better compared side-by-side by the consumer due to these recommendations for regulation. Implementing more effective regulations could actually help

with the innovation of DTC genetic tests. For example, having a more streamlined approach could increase the speed of discovery for new genetic-disease correlations or more accurately narrow in existing, complex gene-trait correlations. Insisting that DTC genetic tests use a classification system and have mandated labeling criteria could also increase the participation of the consumer by giving feedback to the company, either directly through communication with the company or indirectly by utilizing their purchasing power. Working collaboratively with medical professionals and consumers, DTC companies could extend their distribution range and sell more products because medical professionals would be more aware of the products on the market and more comfortable speaking about them to consumers. Maintaining regulations that are flexible and adaptable enough for continued evolution of policy as genetics knowledge increases will be important. With these recommendations, direct-to-consumer genetic tests will experience continued innovations and development.

Collaboration between medical professionals, consumers, DTC companies, and governmental agencies could lead direct-to-consumer genetic tests to be widely available and useful to consumers at a low cost. Consumers would then be able to consult with their medical professional for a full interpretation of the results. In the end, the knowledge could benefit society by adding to the greater public health knowledge, leading to treatment or cures for genetic diseases. It is amazing how much a person can learn about themselves by spitting into a tube, and the future of personalized genetics is even more promising!

Appendix A. Customer reviews directly from the 23andMe website on April 21, 2016
(<https://www.23andme.com/reviews/>)

New Hampshire ★★ 2 out of 5 stars. · a day ago

“Great Ethnicity data, rest of reports-not so much”

Ancestry/ethnic data is interesting and well presented (and the main reason I purchased). Most of the reports are not genetic based, but user reported statistical "pseudo science". I have a 60% probability of having dark hair? Gee, thanks, I can look in a mirror and see what I ACTUALLY have. The dozen or so disease marker reports are nice, but are of diseases so rare that they are of limited usefulness.

Primary interest – Ancestry ✗ No, I do not recommend this product.

Response from 23andMe:

Anonymous · Customer Care · 9 hours ago

Thank you for your feedback. The 23andMe Personal Genome Service provides both health and ancestry information in a single service for a single price and is the first and only genetic service available directly to you that includes reports that meet FDA standards. You receive 60+ personalized genetic reports to help you understand what your DNA says about your health, traits and ancestry.

Most human traits are complex, meaning they are not determined by a single factor. Even when we find genetic factors that have a large effect on a trait, they still explain only a portion of it. This means that we can only determine the likelihood of having that trait. That means there is still the chance of not having that trait.

Many other factors influence traits, including your ancestry, other genes, and other non-genetic factors. That’s why we also include a section in each report that talks about some of these other factors. The results are based only on specific genetic factors that we know about now, but our predictions may get better as we learn more.

Chicago, IL, United States ★ 1 out of 5 stars. · 12 hours ago

“\$\$ for detached earlobes?”

I was VERY disappointed in what I received for the money I paid. The Ancestry portion was far too general. I found out that, among other more specific locations, am 38.2% Broadly Northwest European. That is a huge portion of my ancestry that you lumped into a very big area. The Carrier Status report was useless to me as it identified that a variant was not detected for 36 RARE genetic disorders. What about the variant for Alzheimer’s disease (which was included in my son’s report a few years ago) or a disease that might actually afflict a 62 year old woman with 38.2% Broadly Northwest European ancestry? And the Traits report was laughable. Yes, I already knew I have detached earlobes! Signed: an unhappy customer

Primary interest – Ancestry ✗ No, I do not recommend this product.

Fort Worth, TX, United States ★★ 2 out of 5 stars. · 2 days ago
“Disappointing”

I really expected more from the DNA reports. I already knew I was bald and had a propensity for caffeine.

Primary interest – Ancestry ✗ No, I do not recommend this product.

Response from 23andMe:

Anonymous · Customer Care · 9 hours ago

Thank you for your feedback. The 23andMe service includes reports that meet FDA standards. You receive more than 60 personalized genetic reports that include health, wellness, ancestry, and trait reports. The service also includes access to interactive tools to share and compare with friends and family.

Colorado ★★ 2 out of 5 stars. · 3 days ago
“More \$ for the info.”

So i bought this for medical reasons and now I have to pay \$350 for a doctor to tell me the results of things I have or may be. Very frustrating. I guess it works but if you want info other than ancestry be prepared to pay for it.

Primary interest – Health ✓ Yes, I recommend this product.

Response from 23andMe:

Anonymous · Customer Care · 9 hours ago

Thank you for your feedback. The new 23andMe experience is the first and only genetic service available directly to you that includes reports that meet FDA standards. You now are able to receive 60+ reports on health, traits and ancestry instead of exclusively ancestry reports.

Syracuse, Ny ★ 1 out of 5 stars. · 3 days ago
“Not what I expected.”

This is more novelty than scientific.

I do not like the constant pestering for me to answer questions. If they are going to ask all the questions, they should reimburse me for the test.

It is not precise. An example 70% chance of wet ear wax first off who cares, second off, that is the best you can do.

The only part that is interesting, is the ancestry, and that can be done for half the price. The genetic test can be done via blood test, and done for free by your doctor. Just ask.

Primary interest – Health ✗ No, I do not recommend this product.

Response from 23andMe:

Anonymous · Customer Care · 9 hours ago

Thank you for your feedback. The 23andMe Personal Genome Service provides both health and ancestry information in a single service for a single price and is the first and

only genetic service available directly to you that includes reports that meet FDA standards. You receive 60+ personalized genetic reports to help you understand what your DNA says about your health, traits and ancestry.

In addition, you can access interactive tools to share, compare and discover more with friends and family.

The data that we report is strictly genetic information regarding your genotype (e.g. the A's, T's, C's, and G's at particular locations in your genome), generated through processing of your saliva by 23andMe. Participation in surveys is completely voluntary. Choosing not to participate will not affect your genetic data.

Maryland, United States ★★ 2 out of 5 stars. · 5 days ago
“Things that no one would care about”

I thought this DNA test would provide me with what types of food I should eat and avoid. What type of exercise is most suited for me and so forth. Instead I got what type of earlobe I have. What cares.

Primary interest – Health No, I do not recommend this product.

Response from 23andMe:

Anonymous · Customer Care · 9 hours ago

Thank you for your feedback. The 23andMe Personal Genome Service provides both health and ancestry information in a single service for a single price and is the first and only genetic service available directly to you that includes reports that meet FDA standards. You receive 60+ personalized genetic reports to help you understand what your DNA says about your health, traits and ancestry.

We will continue to work with the FDA to seek additional clearances for our product. However we are not able to speculate about changes to reports, or what may be available in the future, given our dialogue with the FDA is ongoing.

West Coast, America ★ 1 out of 5 stars. · 5 days ago
“No value added”

The only specific information I have received so far is that I am 99.8% European, don't have a proclivity for any of the obscure diseases listed and my second toe probably isn't longer than my first....really? What part of Europe? what about cancer, diabetes, dementia ?? This all appears to be only a 'connecting tool' for marketing purposes. Not interested.

Primary interest – Ancestry No, I do not recommend this product.

Response from 23andMe:

Anonymous · Customer Care · 9 hours ago

Thank you for your feedback. We do not currently offer reports on hereditary risks for diseases like cancer, heart disease and other serious health risks.

Appendix B. Table summarizes policy recommendations from other professional organizations (Caulfield and McGuire, 2012)

| Professional Organization | Year | Policy Recommendations | | | | |
|---|-------------|---|--|--|---|--|
| Secretary’s Advisory Committee on Genetics, Health, and Society | 2010 | Improve federal oversight | Include DTC tests in the federal test registry | Evaluate DTC company claims using a federal task force | Address gaps in privacy and research protections | Develop genetics education for consumers and health professionals |
| American College of Medical Geneticists (ACMG) | 2008 | Involve knowledgeable professionals in testing | Inform consumers about benefits and limits of tests | Clearly state the scientific basis of tests | Testing laboratories must be accredited by a relevant authority | Discuss privacy issues before testing |
| American Medical Association (AMA) | 2008 | Testing supervised by a qualified health professional | Consumers should seek health professional advice before buying tests | AMA provide input on acceptable marketing | Federal authorities should ensure company claims are fair and truthful | AMA inform members about DTC issues to support patient education |
| American Society of Human Genetics (ASHG) | 2007 | Transparency from companies about scientific basis for tests and advice | Regulatory action by the federal government to ensure test and lab quality | Educate members of health professional organizations about DTC tests | Companies must protect privacy and explain compliance with applicable law | Further research needed on evidence base for tests and impact of DTC access on consumers |

Appendix C. Questionnaire presented to interviewed professionals

1. How familiar are you with predictive genetic testing?
Not very Somewhat Very

Describe.
2. How familiar are you with the following companies: deCODEme, 23andMe, etc.?
Never heard of A little Somewhat Very
3. The above companies offer direct-to-consumer (DTC) predictive genetic tests to assess the level of risk associated with diseases for an individual. As a clinician/genetic counsellor/bioethicist/legislator, do you have concerns with this method of testing?
Yes No

Describe.
4. Do you feel DTC predictive genetic tests are accurate and reliable?
Yes No

Explain.
5. What do you think the average person understands about how genetic and environmental factors influence health?
6. Who should be responsible for ensuring that results are conveyed in an easy to understand format?
 - a. Company
 - b. Congress
 - c. Consumer
 - d. Government agency(ies) (e.g. – FDA)
 - e. Professional organization(s) (e.g. – AMA)
 - f. Researchers
Why?
7. Should policy surrounding DTC predictive genetic testing be determined by the market or by government regulations? Why?
8. What elements would you include in your conversation with a patient/client/constituent who was interested in predictive genetic testing?
9. What would be the three most important factors to you for a policy regulating DTC predictive genetic testing?
10. Would you recommend using DTC predictive genetic testing? Why or why not?

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