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BRCA1 and BRCA2 Mutation Carrier Perspectives on Direct-To-Consumer Genetic Testing for Brca Mutations

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BRCA1 AND *BRCA2* MUTATION CARRIER PERSPECTIVES ON DIRECT-TO-CONSUMER GENETIC TESTING FOR BRCA MUTATIONS

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ABSTRACT

Recently the FDA authorized one direct-to-consumer genetic testing (DTC-GT) company to begin reporting certain genetic variants in the *BRCA1* and *BRCA2* genes. Pathogenic variants in these genes confer lifetime risks for breast and ovarian cancer in women as high as 87% and 62%, respectively. Historically, genetic testing for these mutations has been offered in a clinical setting where genetic counseling is part of the testing process. Genetic counseling is not routinely a part of DTC-GT, raising concern that those undergoing DTC-GT for *BRCA1/2* mutations may not fully understand what is being tested, the implications of results, or that they may experience psychological distress from receiving an unexpected result. The goal of our study was to assess how *BRCA1/2* mutation carriers who went through clinical genetic testing feel about DTC-GT for *BRCA1/2* mutations. Results indicate that most respondents are in favor of DTC-GT for *BRCA1/2* mutations being available, as it increases access to this empowering information. However, most participants also had concerns about DTC-GT, with most worried about false negatives and lack of counseling/support for mutation-positive consumers. Additionally, respondents would be more likely to choose DTC-GT in a scenario where clinical testing is difficult to access or when they had negative perceptions of certain aspects of their own genetic testing experience. These findings suggest that an enhanced DTC-GT model which incorporates pre- and/or post-test counseling by a certified genetic counselor could be a viable option that would have support from the BRCA-mutation carrier population.

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BACKGROUND

1.1 Direct-to-consumer genetic testing

Genetic testing has evolved rapidly since it was first utilized in the 1960s. Over the past few decades, more tests have become available and are being offered at a lower price than previously. Historically, genetic testing has been ordered by physicians, genetic counselors, or other healthcare providers to evaluate future risk of a specific disease, establish a diagnosis, or aid in medical management of an existing condition. In this setting, the healthcare provider determines which genetic test fits the patient's needs and desires, collects the sample, sends it to a laboratory to be analyzed, and then delivers the results to the patient. Typically, this process also involves some form of genetic counseling—performed by either the ordering provider or a board-certified genetic counselor. Genetic counseling helps the patient understand the test itself, their result, and what it means for their health, but can also have a role in assessing and managing the patient's psychological response.

Direct-to-consumer genetic testing (DTC-GT) is a process by which individuals can order genetic testing without involvement of their personal physician or healthcare provider. Since DTC-GT first entered the market in the mid-2000s, it has grown quickly and is expected to continue to grow at a rate of 20% over the next eight years ("Direct-To-Consumer…", Credence Research). DTC-GT can be ordered by any adult via the

internet, phone, or over-the-counter (Wesselius & Zeegers, 2013). Once a person orders the test, a collection kit is usually sent to their home. A saliva sample is then sent back to the company for analysis. Results are typically reported back to the consumer within 8 weeks. Information provided through DTC-GT can include ancestry, physical traits, genetic disease risk, and carrier status (Wesselius & Zeegers, 2013). While the process up to this point usually does not involve the patient's healthcare provider, some patients may share their results with their provider, and some DTC-GT companies offer post-test genetic counseling to consumers. However, research has shown that few customers utilize post-test genetic counseling (Koeller et al., 2017). Additionally, the cost of DTC-GT has significantly decreased since it first became available, from around $1,000 in 2007 to approximately $100-150 today (Allyse et al., 2018). This allows many patients to order DTC-GT without relying on health insurance.

1.2 Potential benefits of direct-to-consumer genetic testing

DTC-GT has several potential advantages and benefits over clinical genetic testing, which have contributed to its rapid growth over the past decade. One of the main benefits is accessibility. Certain information that is offered through DTC-GT, such as carrier status for genetic conditions, or testing for alleles associated with increased risk for certain conditions, can otherwise only be ordered through genetic professionals. However, there is currently a shortage of geneticists and genetic counselors in the United States, making it difficult for many people to have access to their services (Hoskovec et al., 2018). In some areas, people may have to drive hours to meet with a geneticist or genetic counselor, and others may have to wait months to get an appointment. With DTC-

GT, anyone who has access to a phone or to the internet can obtain certain genetic information without needing access to a genetics professional.

Additionally, cost is a major issue for many people who desire genetic information. The 23andMe health and ancestry kit, for example, typically costs about $200USD, while a carrier screening panel that screens for a similar number of conditions from a clinical lab may cost thousands of dollars. For those with no or limited insurance coverage, DTC-GT may be a more feasible option than pursuing clinical genetic testing.

Proponents of DTC-GT also argue that the increased accessibility of genetic information with DTC-GT will allow the general population to be more engaged in their healthcare, more autonomous in health-related decision-making, and more knowledgeable about hereditary disease. By providing people with information about their genetic susceptibility to disease, DTC-GT empowers patients to make informed health-related decisions. One recent study on DTC-GT found that after receiving results, 59% of DTC-GT customers surveyed said that their test results would influence how they manage their health, and 65% said they felt more in control of their health after receiving results (Roberts et al., 2017). Many healthcare providers also agree that information provided by DTC-GT can be useful information for consumers, especially when it comes to testing for hereditary cancer syndromes. For example, 86% of providers surveyed in one study agreed that DTC-GT for hereditary breast cancer provides clinically useful information (Giovanni et al., 2010). Research has also shown that individuals who learn that they are at high risk for cancer after genetic testing often find the information useful and empowering (Crotser and Dickerson, 2010). In a survey of people who learned of their risk for hereditary cancer through DTC-GT, 97% of consumers were glad they

learned of their increased risk for cancer, and almost every participant who learned of their increased risk for cancer for the first time through DTC-GT made plans to consult specialists, undergo increased cancer screening, or even pursue prophylactic surgery (Francke et al., 2013).

1.3 Potential risks of direct-to-consumer genetic testing

The rapid growth and utilization of DTC-GT has raised concern among some health professionals about the possible risks of this type of unsupervised genetic testing. Some genetic test results can be confusing, upsetting, or life-altering for patients. Concerns include the incorrect comprehension or use of results by patients or that results could cause unnecessary worry and anxiety in patients (Annes, Giovanni, & Murray, 2010; Kalokairinou, Howard & Borry, 2014; "What are the benefits…", 2018). Those patients who do not have high health literacy or a basic understanding of genetics may not understand the complexity of genetic information that is reported via DTC-GT or even understand that information they receive from DTC-GT could have a significant impact on their lives. For example, it has been shown that people who ordered DTC-GT report lower levels of confidence in their genetic knowledge and understanding after they go through the process of DTC-GT than they did before undergoing testing, indicating that patients may not fully appreciate the complexities of genetic risk and inheritance prior to ordering DTC-GT (Carere et al., 2016). Additionally, consumer comprehension of results from DTC-GT varies significantly based on demographic factors such as age and level of education (Ostergren et al., 2015). Another major concern is that DTC-GT could burden patients with unnecessary costs as the result of inappropriate follow-up care after misinterpreted test results (Annes, Giovanni, & Murray, 2010). One study found that

clinical follow-up for DTC-GT results, including referral to physicians and/or a genetic counselor, referral to a specialist, and referral for additional diagnostic testing ranged from $40 to over $20,000 (Giovanni et al., 2010). This supports the concern that DTC-GT could result in a high financial burden on the patient and/or healthcare system, especially when DTC-GT results are misinterpreted or have limited clinical utility.

The potential for psychological stress is also a concern with DTC-GT. In one recent study, close to 40% of people who ordered DTC-GT said they did not consider the possibility that they could get information they did not want from the test (Roberts et al., 2017). For example, some consumers may not want to know that they carry a variant that is associated with late-onset Alzheimer's Disease, which is reported by some DTC-GT services. Knowing this information could cause anxiety as well as fear that they might develop Alzheimer's, for which there are no preventative measures or cure. While these sorts of concerns are routinely discussed when genetic testing is ordered through a health professional, many consumers likely do not consider this possibility when ordering DTC-GT. In a case report published by Dohany and colleagues (2012), one patient unexpectedly found out via DTC-GT that she had an Ashkenazi Jewish founder mutation that significantly increased her risk for breast and ovarian cancer. This patient stated that this was not information she had been prepared or wanted to receive, and it caused her psychological distress, resulting in constant worrying and loss of sleep. She also had trouble understanding the meaning of her results and how she should proceed with her management (Dohany et al., 2012). Although this particular patient eventually sought genetic counseling, which alleviated much of her anxiety and confusion, it appears that the majority of people who receive DTC-GT do not discuss their results with a healthcare

provider. In fact, one previous study found that only 4% of people who went through DTC-GT planned on scheduling an appointment with a genetic counselor to discuss the results (Koeller et al., 2017).

The American College of Medical Genetics and Genomics (ACMG) has published a position statement with recommendations regarding DTC-GT. Recommendations include involving a professional when ordering the test and when delivering and interpreting results, inclusion of family history when calculating disease risk, and clearly stating what DTC-GT can and cannot definitively tell the consumer about health and disease risk (ACMG Board of Directors, 2016). However, many consumers do not involve healthcare providers at all in the DTC-GT process, and most DTC-GT companies do not take family history into account when calculating disease risk. The position of the National Society of Genetic Counselors is that consumers have a right to make an informed decision regarding DTC-GT, and companies offering DTC-GT have a responsibility to offer genetic counseling services or referral to such services (NSGC, 2015).

1.4 FDA regulation of direct-to-consumer genetic testing

The U.S. Food and Drug Administration (FDA) began regulating DTC-GT in 2010, after an investigation by the U.S. Government Accountability Office concluded that DTC-GT companies used deceptive marketing and gave misleading test results that exaggerated the utility of the information provided by the test results in relation to health (Allyse et al., 2018). Additionally, other critics of DTC-GT were concerned that the informed consent process for testing was unclear and that consumers may not fully understand the implications of their test results (Skirton et al., 2012). This investigation

prompted the FDA to send warning letters to the five largest DTC-GT companies (23andMe, Navigenics, deCODE Genetics, Knome, and Illumina) in June 2010, informing them that their health-related testing services needed FDA approval prior to marketing them to the general public. The FDA sent another letter in 2013 to several DTC-GT companies, including 23andMe, that had failed to comply with the requests made by the FDA in 2010. In this 2013 letter, the FDA ordered them to stop marketing and selling their DTC-GT services for health-related information, such as breast cancer risk, until appropriate studies on the validity had been performed and the FDA approved them (Allyse et al., 2018). The FDA cited concern that people may make drastic health-related decisions based on their test results, particularly results related to breast cancer risk, and that there was no evidence that the genetic testing being performed was analytically or clinically valid (Annas and Elias, 2014). This was a major step in the regulation of DTC-GT.

Over the next few years following the FDA shutdown of DTC-GT, 23andMe worked to ensure the validity of its tests as well as conduct research on user comprehension of results (Allyse et al., 2018). The first FDA approval of a DTC-genetic test came in 2015, when 23andMe received approval to market a test to screen for carriers of the genetic disease Bloom Syndrome (Allyse et al., 2018). DTC companies were then approved to offer carrier screening for additional diseases as well, and in 2017 the FDA authorized DTC-GT companies to begin offering tests for "genetic health risk" (Allyse et al., 2018). 23andMe was the first company to begin marketing this type of test, offering reports for some treatable or preventable diseases, such as celiac disease and hereditary hemochromatosis, as well as some potentially life-shortening, incurable disorders such as

Alzheimer's disease and Parkinson's disease. The reports for non-curable diseases such as Alzheimer's and Parkinson's are "opt-in", meaning that customers will not be shown their results unless they choose to see them and those that do choose to see them must read a disclaimer prior to being shown their results. Additionally, for each genetic health risk report, the company makes clear that receiving a result indicating that you are at high risk to develop a certain disease does not mean you will definitely develop the disease. In 2018, the FDA gave approval to 23andMe to begin opt-in reporting on certain variants in breast cancer susceptibility genes *BRCA1* and *BRCA2* (US Food and Drug Administration, 2018). Most recently, in January of 2019, the FDA gave clearance for 23andMe to begin reporting two additional cancer risk variants in the *MUTYH* gene, which is associated with a hereditary colorectal cancer syndrome.

Some research has been done investigating public opinion of expanded access and government regulation of DTC-GT. In one study, people who sought DTC-GT were generally in favor of expanded access and less government regulation (Gollust et al., 2017). However, consumers who believed their results indicated that they were at higher risk for a genetic disease and consumers who reported negative emotions after receiving their results were less likely to support expanded access to DTC-GT without involving a healthcare professional (Gollust et al., 2017).

1.5 Breast cancer and *BRCA1* and *BRCA2* mutations

Breast cancer is the most common cancer in the world, affecting 1 in 8 women in their lifetime and is the leading cause of cancer-related death in women. It is estimated that about 10% of breast cancer is caused by familial mutations in single genes. Mutations in the *BRCA1* and *BRCA2* genes are thought to be responsible for about 50%

of cases of hereditary breast and ovarian cancer (HBOC), and about 5-6% of all breast cancers (Campeau et al., 2008). *BRCA1/2* mutations are highly penetrant and inherited in an autosomal dominant fashion. This means that a mutation in only one copy of the *BRCA1* or *BRCA2* gene is sufficient to cause an increased cancer risk. Additionally, each person with a *BRCA1/2* mutation has a 50% chance of passing the mutation on to each of their children.

The lifetime risk of a woman with a *BRCA1/2* mutation developing breast cancer is estimated to be between 38% and 87%, compared to 12% in the general population. A woman with a *BRCA1/2* mutation also has a lifetime ovarian cancer risk of 16.5% to 62%, compared to 1-2% in the general population (Petrucelli, Daly & Pal, 2016). Men with *BRCA1* or *BRCA2* mutations are also at an increased risk for breast cancer. In the general population, about 0.1% of males will develop breast cancer while 1.2% of men with a *BRCA1* mutation and 8.9% of men with a *BRCA2* mutation will develop breast cancer in their lifetime (Petrucelli, Daly & Pal, 2016). Additionally, people with *BRCA1/2* mutations are also at increased risk to develop other types of cancers. Men with *BRCA1/2* mutations have an 8-20% lifetime risk of developing prostate cancer, compared to a 6% chance in the general population (Petrucelli, Daly & Pal, 2016). The risk for pancreatic cancer is also increased in individuals that carry a mutation in *BRCA1/2*.

1.6 Genetic testing for *BRCA1* and *BRCA2* mutations

Analysis of the *BRCA1* and *BRCA2* genes is one of the oldest and most well-studied uses of clinical genetic testing for hereditary cancer risk. Indications for genetic testing of *BRCA1/2* mutations include a strong family history of breast and/or ovarian cancer, unusual presentations of breast cancer (for example, a male with breast cancer),

early-onset breast cancer, a mutation previously identified in the family, or Ashkenazi Jewish ancestry with any breast cancer family history, as the frequency of *BRCA1/2* mutations is higher in this population (Hampel et al., 2015). Genetic testing for *BRCA1/2* mutations usually begins with an in-depth discussion of personal and family history and risk assessment. If the decision to order genetic testing is made, the healthcare provider typically helps the patient choose between testing for mutations in *BRCA1*/2 only or testing for mutations in a panel of genes (including more than just *BRCA1/2*) that are known to be associated with hereditary breast and/or ovarian cancer. Targeted testing for known familial mutations can also be done. If a patient tests positive for a *BRCA1* or *BRCA2* mutation, professional guidelines outline a number of actions that can be taken to reduce risk or improve detection of breast and ovarian cancer, including increased screening (such as mammograms and breast MRI), risk-reduction agents such as tamoxifen, and in some cases prophylactic surgery, such as bilateral mastectomy or salpingo-oophorectomy. It is also recommended that women who undergo testing for *BRCA1/2* mutations receive counseling about cancer risk, management techniques, and psychosocial issues, as deciding to undergo prophylactic surgery can be stressful and significantly impact quality of life (National Comprehensive Cancer Network, 2017).

Testing positive for a *BRCA1* or *BRCA2* mutation can have a psychological impact on a patient. In one study, 75% of patients reported that their worry increased after receiving their positive test results. The patients reported anxiety over the high possibility of getting cancer and worry about passing on the mutation to their children (Prospero et al., 2001). Other studies have also found that patients who receive a positive test result tend to experience increased levels of anxiety and depression compared to

patients with a negative test result (Lodder et al., 2001; Wagner et al., 2000). In one study examining patient satisfaction with Ashkenazi Jewish population-level carrier screening for *BRCA1/2* mutations, each of the 26 participants interviewed reported a need for psychological support after receiving a positive test result (Lieberman et al., 2017). In addition to the anxiety that many women experience after learning they carry a *BRCA1/2* mutation, they also may experience feelings of stress and conflict over deciding whether they should take preventative measures (such as major prophylactic surgery) to reduce their cancer risk (Metcalfe et al., 2016). However, while anxiety and depression may be the most common feelings in patients who learn they carry a *BRCA1/2* mutation, it should also be noted that some patients experience different emotions following a positive *BRCA1/2* test result, including feelings of empowerment (Crotser & Dickerson, 2010) and even relief as a positive result can give them an explanation for why many members of their family developed cancer.

1.7 Direct-to-consumer genetic testing for *BRCA1* and *BRCA2* mutations

In March 2018, 23andMe received FDA approval to report three *BRCA1/2* mutations through their service (US Food and Drug Administration, 2018). 23andMe had originally reported these *BRCA1/2* gene variants as part of their previous DTC-GT product until the FDA prohibited reporting of these results in 2013 and requested confirmation of analytic and clinical validity. Today, anyone who purchases 23andMe's health and ancestry service can access their *BRCA1/2* results. One major caveat of this service is that 23andMe only reports on three out of hundreds of known mutations in *BRCA1/2*. These particular mutations are typically seen in the Ashkenazi Jewish population and are present at very low frequency in the general population (Struewing et

al., 1995; Roa et al., 1996; Oddoux et al., 1996). This means that many people who do in fact carry a pathogenic mutation in *BRCA1* or *BRCA2* will receive a negative *BRCA1* and *BRCA2* result from 23andMe based on testing of the three Ashkenazi Jewish founder mutations alone.

Physicians in recent publications have debated the risks and benefits of DTC-GT for *BRCA1/2* mutations. One physician, a surgical oncologist, says that DTC-GT for *BRCA1/2* mutations will allow more people who could benefit from this information get tested, because it removes certain barriers to testing such as cost, location, and availability of genetic counselors. He says, "The faster we start letting people know what their specific problems might be, the better off our health is going to be." On the other hand, this particular article also cited a professor of genetics who is not in favor of DTC-GT for *BRCA1/2* mutations, expressing worry over possible misinterpretation of results by consumers, or misunderstanding that results are only reported for three of the many mutations in *BRCA1* and *BRCA2* (American Association for Cancer Research, 2018).

Some limited research on DTC testing for *BRCA1/2* mutations exists. In a study published in 2011, the researchers investigated how women who had family histories of breast and/or ovarian cancer felt about direct-to-consumer advertising for *BRCA1/2* testing and online availability of genetic testing. The women included in this study were at high-risk for breast and/or ovarian cancer based on their family histories and a subset of these women had undergone genetic testing, and a smaller subset had tested positive. While the most women in this study were in favor of direct-to-consumer *advertising* for *BRCA1/2* testing because they felt it would allow women to be better informed and proactive when it comes to their cancer risk, they were generally not in favor of genetic

testing being available for the average person to order online (Perez et al., 2011). The women in the high-risk clinic preferred that testing and decision-making still only be performed with the help of a physician, with 73.8% of women agreeing that testing should only be performed if the patient sees an expert in-person who can counsel them about their breast cancer risk (Perez et al., 2011). This suggests women who are at high risk for breast and ovarian cancer believe that online *BRCA1/2* mutation testing could come with more risks to consumers than benefits if a physician or genetic counselor is not involved in the process. However, since the majority of of these women had never received a positive test result, they may have had a limited understanding of the implications, follow-up, and psychological challenges that come with a positive genetic test result. Additionally, this study mainly focused on attitudes towards direct-to-consumer *advertising* for *BRCA1/2* testing and gathered little information about how these women felt about the genetic testing itself being offered in a direct-to-consumer matter.

One study published in 2013 by Francke and colleagues investigated consumer response to 23andMe's initial phase of reporting *BRCA1/2* mutation results. This study interviewed 32 people who found out they were carriers of a *BRCA1* or *BRCA2* mutation through DTC-GT. Most notably, none of these participants reported being "extremely upset" by their result with most women and men who received a positive result reporting that they had "neutral" feelings. Additionally, most people who received a positive result shared their results with other relatives, and most also brought their results to a healthcare provider for more information and confirmation. Many of the women who learned of their mutation for the first time via 23andMe made decisions regarding their health after

confirmation testing, including prophylactic surgeries or increased screening. Thirty of the thirty-two mutation-positive patients interviewed also said that they would get tested in this manner again as they felt the information was useful and potentially life-saving. Only one participant in this study reported a negative response to learning their test result, saying that knowing he was mutation-positive and could pass it on to his children had a large emotional impact on him (Francke et al., 2013).

While this previous study offers evidence that DTC-GT for *BRCA1/2* mutations may not be as harmful to consumers as some have suggested, it did harbor some significant limitations. One limitation is that the study sample was small, and half of the participants who were interviewed regarding their positive results were men. This is important to note, since men with a *BRCA1* or *BRCA2* mutation have a much lower risk for cancer than women with a mutation and have different motivations for undergoing testing (Liede et al., 2000). Men are more likely to cite concern for their family members and children as reasons for pursuing genetic testing for hereditary cancer, rather than concern for their own personal risk which is the most common reason cited by women (Liede et al., 2000). Additionally, some research has shown that men are less likely than women to experience anxiety or psychological distress after receiving a positive *BRCA1/2* test result, perhaps due to their lower risk for cancer than female mutation carriers (Watson et al., 2004). Additionally, some of the women and men included in this study had already known about a *BRCA1* or *BRCA2* mutation in their family or been diagnosed with a mutation already in themselves. Finally, these patients may not understand the major benefits or limitations of getting tested via DTC-GT in comparison

to the clinical setting, as most of these patients did not experience the clinical testing process (Francke et al., 2013).

1.8 Rationale and study aims

DTC-GT is expected to grow, as is the demand for at-home genetic testing. Currently, genetic counseling is not routinely a part of the DTC-GT process, and many patients go through the DTC-GT process without formal genetic counseling pre-test or post-test. This has raised concern that consumers undergoing DTC-GT for *BRCA1/2* mutations may not fully understand what is being tested, the implications of positive or negative results, or that they may experience psychological distress from receiving a test result that they were not prepared for (Kalokairinou, Howard & Borry, 2014).

While previous studies have examined consumer perspectives of DTC-GT (Carere et al., 2016; Ostergren et al., 2015; Roberts et al., 2017) and one study specifically examined consumer perspectives of DTC-GT for *BRCA1*/2 mutations (Francke et al., 2013), no study to our knowledge has specifically examined the perspectives of patients who have been diagnosed with a *BRCA1* or *BRCA2* mutation via the traditional clinical process on this test being offered through a DTC model. These patients who have been through formal, traditional genetic testing are in a unique position to offer perspectives on DTC-GT for *BRCA1/2* mutations. It may be that that some people who have been diagnosed with *BRCA1*/*2* mutations through in-person genetic counseling are in favor of the testing being available through DTC-GT. We know that the information is useful, empowering, and potentially life-saving (Crotser and Dickerson, 2010), so some would argue that it should be available to everyone, regardless of whether they are able to access a genetic counselor or have insurance. On the other hand, other

patients may feel as though the process of going through testing and getting a positive result was so confusing, difficult, and stressful that it should not be available for any person to order from home without input or consent from a physician.

The goal of the present study is to investigate the attitudes of *BRCA1/2* mutation carriers regarding DTC-GT for *BRCA1/2* mutations. A better understanding of patients' attitudes and feelings about DTC-GT for *BRCA1* and *BRCA2* mutations will have implications in the fields of genetics, oncology, genetic counseling, and public health. To investigate these topics, this study has three specific aims:

Among *BRCA1/2* mutation carriers identified through clinical genetic testing:

1. Evaluate attitudes towards the availability of direct-to-consumer testing for *BRCA1* and *BRCA2* mutations.
    - Hypothesis: The majority of *BRCA1/2* carriers surveyed will be in favor of DTC-GT for *BRCA1/2* mutations
2. Investigate which aspects of the clinical genetic testing process *BRCA1/2* carriers find most and least favorable in comparison to direct-to-consumer genetic testing, and in which situations they may opt to choose DTC-GT over clinical testing.
    - Hypothesis: Cost and accessibility will seem favorable in DTC-GT compared to clinical testing, while education provided and psychological support will seem favorable in clinical genetic testing compared to DTC-GT. People will be more likely to opt for DTC-GT when accessibility to clinical testing is low or cost of clinical testing is high.
3. Determine how previous clinical genetic testing experience influences one's views of DTC-GT

- Hypothesis: People who had positive experiences with clinical genetic testing will be less likely to support of DTC-GT for *BRCA1/2* mutations.

The results of this study will help healthcare providers understand what patients think the most favorable and unfavorable aspects of the clinical genetic testing process are in comparison to DTC-GT, revealing the areas where improvements can be made in the clinical process. This information will also indicate what patients perceive the potential risks of DTC-GT for *BRCA1/2* mutations might be, offering insight into how to improve direct-access genetic testing and decrease the potential for adverse experiences and outcomes. It will also help us understand which groups of patients who go through DTC-GT may benefit from genetic counseling pre- or post-test.

CHAPTER 2

BRCA1 AND *BRCA2* MUTATION-POSITIVE PATIENT PERSPECTIVES ON DIRECT-TO-CONSUMER GENETIC TESTING FOR BRCA MUTATIONS[1]

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2.1 Abstract

Recently the FDA authorized one direct-to-consumer genetic testing (DTC-GT) company to begin reporting certain genetic variants in the *BRCA1* and *BRCA2* genes. Pathogenic variants in these genes confer lifetime risks for breast and ovarian cancer in women as high as 87% and 62%, respectively. Historically, genetic testing for these mutations has been offered in a clinical setting where genetic counseling is part of the testing process. Genetic counseling is not routinely a part of DTC-GT, raising concern that those undergoing DTC-GT for *BRCA1/2* mutations may not fully understand what is being tested, the implications of results, or that they may experience psychological distress from receiving an unexpected result. The goal of our study was to assess how *BRCA1/2* mutation carriers who went through clinical genetic testing feel about DTC-GT for *BRCA1/2* mutations. Results indicate that most respondents are in favor of DTC-GT for *BRCA1/2* mutations being available, as it increases access to this empowering information. However, most participants also had concerns about DTC-GT, with most worried about false negatives and lack of counseling/support for mutation-positive consumers. Additionally, respondents would be more likely to choose DTC-GT in a scenario where clinical testing is difficult to access or when they had negative perceptions of certain aspects of their own genetic testing experience. These findings suggest that an enhanced DTC-GT model which incorporates pre- and/or post-test counseling by a certified genetic counselor could be a viable option that would have support from the BRCA-mutation carrier population.

2.2 Introduction

Genetic testing has evolved rapidly since it was first utilized in the 1960s. Over the past few decades more tests have become available and are offered at a lower price than previously. In the mid-2000's, direct-to-consumer genetic testing (DTC-GT) entered the market. DTC-GT allows any consumer over the age of 18 to order certain genetic tests for themselves without needing to involve a clinician. This is in contrast to clinical genetic testing, where a healthcare provider typically provides some form of genetic counseling. During this genetic counseling process, the clinician helps the patient understand the test itself, their result and what it means for their health. They also have a role in assessing the patient's psychological response and addressing concerns or questions that arise.

Information provided through DTC-GT can include ancestry, physical traits, genetic disease risk, and carrier status (Wesselius & Zeegers, 2013). DTC-GT is regulated by the Food and Drug Administration (FDA) and the companies can only report on genetic information that the FDA has approved. While DTC-GT usually does not involve the patient's healthcare provider, some patients may choose to share their results with their provider, and some DTC-GT companies offer post-test genetic counseling to consumers. However, research has shown that few customers utilize post-test genetic counseling, even when it is available (Koeller et al., 2017).

DTC-GT has generated much controversy as it has continued to grow and as the number of tests offered has expanded. Those who support DTC-GT claim that its low cost and easy access increase consumer autonomy and engagement in their healthcare by helping them become more knowledgeable about their genetics. One recent study on

DTC-GT found that after receiving results, 59% of DTC-GT customers surveyed said that their test results would influence how they manage their health, and 65% said they felt more in control of their health after receiving results (Roberts et al., 2017). On the other hand, opponents of DTC-GT have many concerns, including the incorrect comprehension or use of results by patients, or that results could cause unnecessary worry and anxiety in patients (Annes, Giovanni, & Murray, 2010; Kalokairinou, Howard & Borry, 2014; "What are the benefits…", 2018). Those patients who do not have high health literacy or a basic understanding of genetics may not understand the complexity of genetic information that is reported via DTC-GT, or even that information they receive from DTC-GT could have a significant impact on their lives. Previous research has shown that consumers often report lower levels of confidence in their genetic knowledge and understanding after they go through the process of DTC-GT than they did before undergoing testing, indicating that patients may not fully understand the complexities of genetic risk and inheritance prior to ordering DTC-GT (Carere et al., 2016). Additionally, unexpected results may cause anxiety and stress, which has been documented in some cases (Dohany et al., 2012). One study found that close to 40% of people who ordered DTC-GT said they did not consider the possibility that they could get information they did not want from the test (Roberts et al., 2017).

In March 2018, the debate over DTC-GT became more heated when the FDA announced approval for one of the largest DTC-GT companies, 23andMe, to resume reporting on certain pathogenic variants in the *BRCA1* and *BRCA2* genes, which are associated with hereditary breast and ovarian cancer (US Food and Drug Administration, 2018). The company had previously reported on these variants briefly in 2013, until the

FDA prohibited it due to lack of proper validation. With the new approval, anyone who purchases the health and ancestry service through 23andMe for $199 can have access to their *BRCA1/2* report, which looks for three specific pathogenic variants typically found in the Ashkenazi Jewish population.

DTC-GT for *BRCA1/2* mutations has increased worry about this relatively unsupervised form of genetic testing in many professionals. For the past 20 years, *BRCA1/2* testing has been ordered for patients by healthcare providers that take family history and patient preferences into account while also helping patients deal with the significant health-related and psychosocial implications of results. The lifetime risk of a woman with a *BRCA1* or *BRCA2* mutation developing breast cancer is estimated to be up to 87%, compared to 12% in the general population. A woman with a *BRCA1* or *BRCA2* mutation also has a lifetime ovarian cancer risk of up to 62%, compared to 1-2% in the general population (Petrucelli, Daly & Pal, 2016). Men with *BRCA1/2* mutations are at increased risk for breast cancer and prostate cancer, and both men and women are at increased risk for other types of cancer, including pancreatic. In women who test positive for a *BRCA1/2* mutation, national guidelines outline a number of significant changes to medical management, including increased screening, consideration of preventative medications, and consideration of prophylactic removal of the ovaries and/or breasts (National Comprehensive Cancer Network, 2019). With a positive result, many patients experience increased levels of anxiety about developing cancer and about passing on the mutation to their children (Prospero et al., 2001).

There is a worry that consumers who learn that they carry a *BRCA1/2* mutation though DTC-GT may not fully understand what is being tested for, the implications of

their results, or that they may experience psychological distress from receiving a test result that they were not prepared for (Kalokairinou, Howard & Borry, 2014). Additionally, consumers unfamiliar with genetics may not understand the limitations of the testing. For example, *BRCA1/2* testing offered through DTC-GT only looks for 3 mutations in the *BRCA1* and *BRCA2* genes out of thousands of known mutations, giving many consumers that do carry a mutation a false negative result. Consumers may also not understand the complicated implications of the result without talking to a healthcare provider. However, some professionals are in favor of this increased access to *BRCA1/2* testing, arguing it makes testing more accessible for those who may not have health insurance, access to a genetic counselor, or experience another barrier to clinical testing. Through DTC-GT, more people can learn that they carry a *BRCA1/2* mutation and have the opportunity to act to decrease their risk of developing cancer. A previous study has shown that people who learn they have a *BRCA1/2* mutation view the information as useful, empowering, and potentially life-saving (Crotser and Dickerson, 2010).

Limited research has been done on DTC-GT for *BRCA1/2* mutations. In one study that examined the responses of patients to learning that they carry a *BRCA1/2* mutation through DTC-GT, it was found that no patients reported being "extremely upset" by their result, and that 94% of patients would get tested in this manner again (Francke et al., 2013). However, this study harbored multiple limitations, including that some participants already knew of their mutation status before the test and that over half of the participants were men, who have much lower *BRCA1/2*-associated risks for cancer compared to women. In another study that examined the perspectives of women at high risk for breast or ovarian cancer on DTC advertising and testing for *BRCA1/2* mutations,

it was found that many women are in favor of DTC *advertising* for *BRCA1/2* testing but think that the testing is best done through a healthcare provider (Perez et al., 2011). However, most participants in this study had never tested positive for *BRCA1/2* mutations and some had never even undergone genetic testing and therefore had limited knowledge on the genetic counseling that typically comes with a positive test result. Additionally, this study mainly focused on direct-to-consumer *advertising* for *BRCA1/2* testing, rather than on the genetic testing itself being offered in a DTC-manner.

To our knowledge, no study has specifically examined the perspectives of patients who have been diagnosed with a *BRCA1* or *BRCA2* mutation via the traditional clinical process on this test being offered in a DTC model. These patients who have been through the formal, traditional genetic testing are in a unique position to offer perspectives on DTC-GT for *BRCA1/2* mutations. They know what the traditional testing method has to offer, and also understand the risks and benefits of learning that you carry a *BRCA1/2* mutation. In this study, our objectives were (1) to assess the attitudes of *BRCA1/2* carriers who were diagnosed with clinical testing towards DTC-GT for these mutations, (2) to investigate which aspects of DTC-GT these patients find more or less favorable compared to clinical genetic testing and what factors would motivate consumers to choose DTC-GT rather than clinical testing, and (3) to determine if previous genetic testing experience influences one's views of DTC-GT. The results of this study can help us understand what patients think the most favorable and unfavorable aspects of the clinical genetic testing process are in comparison to DTC-GT, revealing the areas where improvements can be made in the clinical process. This information also indicates what patients perceive the potential risks of DTC-GT for *BRCA1/2* mutations might be,

offering insight on how to improve direct-access genetic testing and decrease the potential for adverse experiences and outcomes.

2.3 Materials and Methods

2.3.1 Participants

Women and men who self-reported to have a *BRCA1* or *BRCA2* pathogenic or likely pathogenic variant were invited to participate in this study. Participants were recruited via social media websites, such as Facebook support groups, and one other online support group. Four different Facebook support groups made for *BRCA1/2* mutation carriers and the national nonprofit group Facing Our Risk of Cancer Empowered (FORCE) were contacted to recruit participants. The questionnaire was posted two to three times in each Facebook support group during the recruitment period, and it was posted on the FORCE Facebook page and FORCE Twitter account once. Recruitment took place from August 2018 through January 2019. Permission was obtained from administrators or representatives of each group prior to posting the questionnaire. The questionnaire was posted in the groups along with a short description of the research and study requirements. Participants were instructed that they could skip any question that made them uncomfortable or that they did not wish to answer. Informed consent was obtained from each participant prior to starting the questionnaire. The questionnaire contained three eligibility questions at the beginning to ensure only responses from the desired population would be obtained: 1) they carried a *BRCA1/2* mutation; 2) they were the first person in their family found to carry this mutation; and 3) their genetic testing was ordered by a healthcare provider, such as an oncologist, surgeon, OB/GYN, family physician, genetic counselor, or nurse. Participants were also required

to be over the age of 18 and English-speaking (due to a lack of translated survey materials). To be included in data analysis, participants must have completed the majority of questions through the end of the questionnaire. While study recruitment was not gender-specific, males were ultimately excluded from data analysis, since there were so few of them (see Results below). Participants were informed that they had the option to be included in a drawing for a $10 Amazon.com gift card upon completion of the questionnaire if they desired. They were also informed that their responses would be anonymous. The winner of the drawing was chosen in February 2019.

2.3.2 Instrumentation

An original questionnaire utilizing skip logic was developed through SurveyMonkey.com (Appendix A). The survey consisted of seven sections: Consent, Eligibility, Demographic Information, Prior Genetic Testing Experience, Direct-to-Consumer Testing Attitudes, Scenarios, and Final Thoughts/Concerns. Section 1 (Consent) included information about the study and the raffle. Consent was assumed upon clicking "OK" at the bottom of the consent page. Those who did not provide consent were not permitted to complete the study. Section 2 (Eligibility) included 3 questions to determine whether participants met eligibility requirements related to genetic testing history (described above). Participants who answered "No" to any of the eligibility questions were routed out of the study. Section 3 (Demographic Information) included nine multiple choice questions to gather information about gender, age, race, country of residence, level of education, household income, and health insurance. Section 4 (Prior Genetic Testing Experience) included Likert scale, select all that apply, and multiple-choice questions to assess how participants viewed their clinical genetic testing

experience. Questions included who ordered the testing, why they were considered for testing, what type of testing was ordered, to what extent their testing was covered by insurance, their wait time for results, and their satisfaction with different aspects of the genetic testing process. For the question asking who ordered the genetic testing, most respondents who selected "other" specified "surgeon", so an additional category for surgeon was created for data analysis. We assessed feelings about their positive result as well as what actions they took after learning their result. We then provided a description of DTC-GT in the questionnaire before asking patients questions pertaining to the topic in Section 5 (DTC Testing Attitudes). This description of DTC-GT included the typical ordering process, cost, how results are delivered and what information results might include. Additionally, information was included about the recent FDA approval of testing for *BRCA1/2* mutations in a DTC manner. Section 5 (DTC Testing Attitudes) consisted of multiple-choice and Likert scale questions to gather information about how participants perceived DTC-GT for *BRCA1/2* mutations, including its benefits and limitations. We also surveyed each participant's familiarity with DTC-GT and whether they had previously undergone any sort of DTC-GT themselves. Section 6 (Scenarios) included multiple Likert scale questions relating to different scenarios (for example, if they had the option to pursue clinical testing for $300 or DTC-GT for $99), and whether the participant would choose DTC-GT or clinical genetic testing in each scenario, with the option to leave additional open comments for each question. Section 7 (Final Thoughts/Concerns) included two multiple-choice questions with the option to include comments. These final questions were meant to obtain participants' final thoughts on the use of DTC-GT for *BRCA1/2* mutations and whether they had any concerns. Overall, the

questionnaire contained 30 questions (excluding eligibility questions) and was designed to take 10-15 minutes to complete. The questionnaire in its entirety is included in Appendix A.

2.3.3 Statistical analysis

Quantitative questions were analyzed using descriptive statistics. For demographic questions and questions pertaining to previous genetic testing experience, data produced was categorical. Frequencies and percentages were calculated for all quantitative questions to summarize participants' responses. For Likert scale (Likert scale: 1-5) questions related to patient satisfaction, favorability of DTC-GT compared to clinical testing, hypothetical scenarios, and support/concerns about DTC-GT, means were calculated in order to obtain average overall scores related to these topics. To test our hypothesis that a positive previous genetic testing experience would influence whether participants were in favor of DTC-GT, a Pearson's product-moment correlation was used to determine whether satisfaction with any aspect of previous genetic testing experience (survey items 15-17) was correlated with whether participants overall supported DTC-GT, had concerns about DTC-GT, or whether they would have chosen DTC-GT or clinical genetic testing for themselves if given the opportunity to choose again. Additionally, as an exploratory exercise, a Pearson's product-moment correlation was used to determine whether any demographic factor (survey items 1-9) or favorability of DTC-GT compared to clinical genetic testing (survey item 22) was correlated with whether participants overall supported DTC-GT or had concerns about it. All correlations were univariate and unadjusted for other variables. SPSS software was utilized for data analysis and the alpha level for statistical testing was set at 0.05. For open response

comments, thematic analysis was performed to identify themes across responses for each question.

2.4 Results

2.4.1 Exclusion and Demographic Information

A total of 288 individuals began and consented to the survey. Of these, 188 participants completed the three eligibility questions and qualified for inclusion in the study. On average, participants spent about 10 minutes completing the questionnaire. Of the 188 participants who initiated the survey, 33 did not complete it and were excluded from analysis. Due to the small number of male participants (3 of 188), males were excluded from the final analytic sample. Demographic characteristics of the 152 participants included in the analysis are summarized in **Table 2.1**. Most participants were Caucasian (94.1%) and had at least a college degree (69.7%). The ages of participants ranged from 26 to 65 with an average age of 47.26 years. Most (77.6%) participants reported having children, having health insurance (96.1%), and an annual household income of ≥$100,000 (54%). A minority (6.6%) resided outside of the US.

2.4.2 Previous Genetic Testing Experience

On average, participants tested positive for a *BRCA1/2* mutation at an age of 43.7 years (range = 21 to 62). Most patients had their genetic counseling performed by either an oncologist (31.6%), a genetic counselor (36.8%), or an OB/GYN (25%) (**Table 2.2**). Participants were most often referred for genetic testing due to either a personal history of cancer (47%) or a family history of cancer (48.4%). A minority of participants sought genetic testing on their own. The majority (57.9%) of participants stated that they underwent panel testing compared to 31.6% who underwent testing for

Table 2.1 Demographic characteristics of survey participants

Characteristics	Frequency	Percent
Race (n=152)		
White or Caucasian	143	94.1*
Hispanic or Latino	10	6.6
Asian or Asian-American	1	0.7
American Indian or Alaska Native	2	1.3
Another race	1	0.7
Unknown/do not wish to specify	2	1.4
Country of residency (n=152)		
United States	142	93.4
Other	10	6.6
Highest level of education (n=152)		
High school	8	5.3
Some college	37	24.3
College degree	61	40.1
Some graduate school	2	1.3
Graduate/Doctoral/Professional degree	44	28.9
Annual household income (n=152)		
Under $40,000	8	5.3
Between $40,000 and $99,999	62	40.8
Between $100,000 and $199,999	52	34.2
$200,000 or greater	15	9.9
Prefer not to answer	15	9.9
Have children (n=152)		
Yes	118	77.6
No	34	22.4
Health insurance coverage (n=152)		
Yes	146	96.1
No	6	3.9
Age in years (n=152)		
Mean ± standard deviation (range)	47.26 ± 9.7 (26-65)	

*Percentages add up to >100% because participants were told to "Select all that apply"

BRCA1/2 alone. The majority of participants also had their testing fully covered by insurance (70.5%) and waited between 1 and 4 weeks for their results (69.8%).

When asked about overall satisfaction with their genetic testing experience (**Table 2.2**), the vast majority of participants were either somewhat satisfied or very satisfied (82.2% of participants). When asked to rate different aspects of their genetic testing

Table 2.2 Previous genetic testing experience

Aspect of experience	Frequency	Percent
Who ordered the testing (n=152)		
Oncologist	48	31.6*
Genetic counselor	56	36.8
Obstetrician or gynecologist	38	25
Family practitioner	12	7.9
Surgeon	14	9.2
Advanced practice nurse in genetics	1	0.7
Other	6	3.9
How were you referred for genetic testing? (n=151)		
Referred by doctor or other healthcare provider after personal history of cancer	68	45
Referred by doctor or other healthcare provider due to family history of cancer	56	37.1
Referred by doctor or other healthcare provider for another reason	5	3.3
Sought testing on my own due to personal history of cancer	3	2
Sought testing on my own due to family history of cancer	17	11.3
Sought testing on my own for another reason	2	1.3
Type of genetic testing ordered (n=152)		
BRCA1 and *BRCA2* genes only	48	31.6
Panel testing	88	57.9
Unsure/don't remember	16	10.5
How much of testing was covered by insurance (n=149)		
Fully covered	105	70.5
Partially covered (had to pay a co-pay)	35	23.5
Not covered at all (paid out-of-pocket)	9	6
Wait time for results (n=152)		
<1 week	5	3.3
1-2 weeks	39	25.7
2-4 weeks	67	44.1
4-8 weeks	33	21.7
>8 weeks	8	5.3
Satisfaction with genetic testing experience (n=152)		
Very satisfied	75	49.3
Satisfied	50	32.9
Neither satisfied or dissatisfied	18	11.8
Dissatisfied	7	4.6
Very dissatisfied	2	1.3
Feelings after results (Scale of 1-5 with 1 being not at all and 5 being extremely)		
Surprised (mean) (n=150)	3.07	
Upset (mean) (n=148)	3.64	
Relieved (mean) (n=145)	1.86	

*Percentages add up to >100% because participants were told to "Select all that apply"

experience on a scale of 1 (very dissatisfied) to 5 (very satisfied), people rated the ease of accessing a clinic and information provided on *BRCA1/2* genes and cancer highest, with means of 4.38 and 4.15, respectively (**Table 2.3**). People reported being least satisfied with the psychological support provided and the information provided on management/treatment for positive results, with means of 3.16 and 3.84, respectively.

We asked participants about their feelings and actions taken after receiving their positive results. When asked to rate how surprised, upset, and relieved they were on a scale of 1 (not at all) to 5 (extremely), participants were on average moderately surprised (mean= 3.07), moderately upset (mean= 3.64), and were not likely to feel relieved (mean= 1.87).

Table 2.3 Satisfaction with previous genetic testing

Aspect of experience	1 very negative	2	3 neutral	4	5 very positive	Mean Score ± SD
Time to get an appointment (n=150)	4 (2.7%)	8 (5.3%)	29 (19.3%)	34 (22.7%)	75 (50.0%)	4.1 ± 1.1
Ease of accessing a clinic (n=150)	0	2 (1.3%)	30 (20.0%)	27 (18.0%)	91 (60.7%)	4.4 ± 0.8
Cost of testing (n=147)	10 (6.8%)	9 (6.1%)	34 (23.1%)	21 (14.3%)	73 (49.7%)	3.8 ± 1.3
Risk assessment (n=149)	6 (4.0%)	4 (2.7%)	34 (22.8%)	25 (16.8%)	80 (53.7%)	4.1 ± 1.1
Information/education on *BRCA1/2* (n=150)	4 (2.7%)	13 (8.7%)	19 (12.7%)	35 (23.3%)	79 (52.7%)	4.1 ± 1.1
Psychological support (n=147)	22 (15.0%)	25 (17.0%)	40 (27.2%)	27 (18.4%)	33 (22.4%)	3.2 ± 1.4
Information on management (n=149)	5 (3.4%)	20 (13.4%)	29 (19.5%)	35 (23.5%)	60 (40.3%)	3.8 ± 1.2
Risk estimation for other family members (n=150)	6 (4.0%)	12 (8.0%)	36 (24.0%)	41 (27.3%)	55 (36.7%)	3.8 ± 1.1

SD= standard deviation

After receiving results, the most common actions taken were prophylactic surgery (75.0%) and communication of results to other family members (71.1%).

2.4.3 DTC-GT Familiarity and Attitudes

Prior to completing our study, the majority of participants either knew what DTC-GT was (57.6%) or had familiarity with the term but weren't sure what it meant (15.9%). About one quarter of participants (23.2%) had undergone DTC-GT before, such as 23andMe or Ancestry DNA. If participants had been given the option between DTC-GT and clinical genetic testing at the time they were undergoing their testing, most participants indicated that they would have definitely or probably chosen clinical testing (80.3%), and 12.0% were not sure which they have chosen. The remaining 6.7% said they would have probably or definitely chosen DTC-GT (Figure 2.1).

2.4.4 DTC Testing vs Clinical Testing

We asked participants to compare different aspects of DTC-GT to clinical genetic testing. The results are displayed in **Table 2.4.** Participants thought the accessibility of DTC-GT was increased compared to clinical genetic testing. However, on average participants rated information/education provided in DTC-GT and psychosocial support provided in DTC-GT lower that what is provided in clinical testing.

2.4.5 Scenarios

We presented participants with different scenarios related to pursuing *BRCA1/2* testing. We asked participants to indicate whether they would have chosen DTC-GT or clinical genetic testing in each scenario on a scale of 1 (definitely clinical) to 5 (definitely

DTC). The results are presented in **Figure 2.1.** Participants more frequently preferred DTC-GT when the cost was significantly cheaper ($99 DTC vs $250-400 clinical), with

Table 2.4 DTC-GT compared to clinical testing

	1 very unfavorable compared to clinical	**2**	**3 same as clinical**	**4**	**5 very favorable compared to clinical**	**Mean Score ± SD**
Cost of DTC (n=143)	33 (23.1%)	17 (11.9%)	26 (18.2%)	28 (19.6%)	39 (27.3%)	3.2 ± 1.5
Accessibility of DTC (n=141)	8 (5.7%)	12 (8.5%)	33 (23.4%)	41 (29.1%)	47 (33.3%)	3.8 ± 1.2
DTC turnaround time (n=137)	9 (6.6%)	19 (13.9%)	89 (65.0%)	12 (8.8%)	8 (5.8%)	2.9 ± 0.9
DTC education/ information provided (n=140)	71 (50.7%)	40 (28.6%)	24 (17.1%)	4 (2.9%)	1 (0.7%)	1.7 ± 0.9
Psychosocial support in DTC (n=139)	81 (58.3%)	35 (25.2%)	19 (13.7%)	3 (2.2%)	1 (0.7%)	1.6 ± 0.9

SD= standard deviation

52% saying they would definitely or probably prefer DTC in this scenario. However, 86.7% of participants definitely or probably preferred clinical testing if the mutation carrier detection rates for DTC-GT and clinical testing were 15% and 95%, respectively. They also more frequently said they would recommend clinical testing for their friend, even if the friend may not meet clinical testing criteria, with 87.4% of participants saying they would definitely or probably recommend clinical testing. For the other scenarios presented, responses were relatively evenly distributed between preferring DTC-GT and clinical testing. When asked if their children desired to pursue DTC-GT rather than clinical testing to see if they carried the same mutation that they had, 66.9% participants indicated that they would probably or definitely support their child's decision.

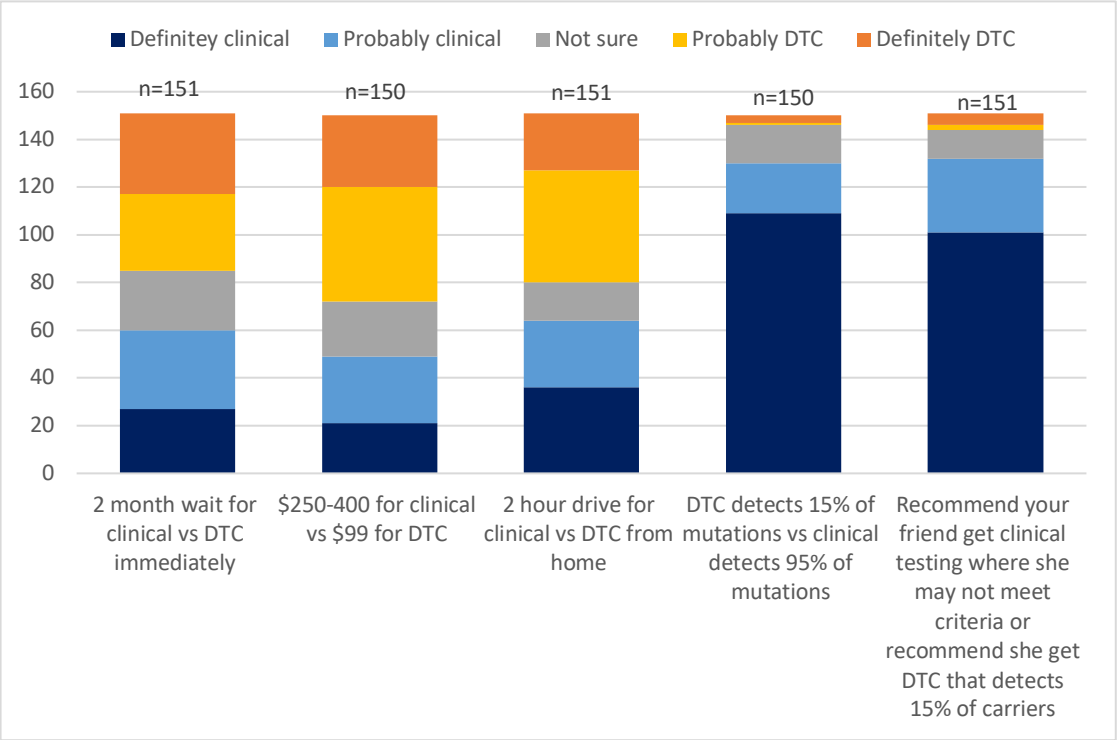

Figure 2.1 *BRCA1/2* carrier preference between DTC-GT and clinical genetic testing in different scenarios

2.4.6 Overall support and concerns

Finally, we asked participants whether they were overall in support of DTC-GT for *BRCA1/2* mutations being available to the general public. Results are displayed in **Figure 2.2**. The majority of respondents indicated that they either somewhat or strongly supported DTC-GT availability for *BRCA1/2* testing (52%), while 25.7% were undecided and 22.3% were somewhat or strongly against it. When asked whether they had concerns about DTC-GT being available, 69.7% of participants indicated that they were either "moderately" or "extremely" concerned about DTC-GT for *BRCA1/2* mutations without involvement from a healthcare provider while 17.1% of participants indicated that they were not concerned or that they were undecided.

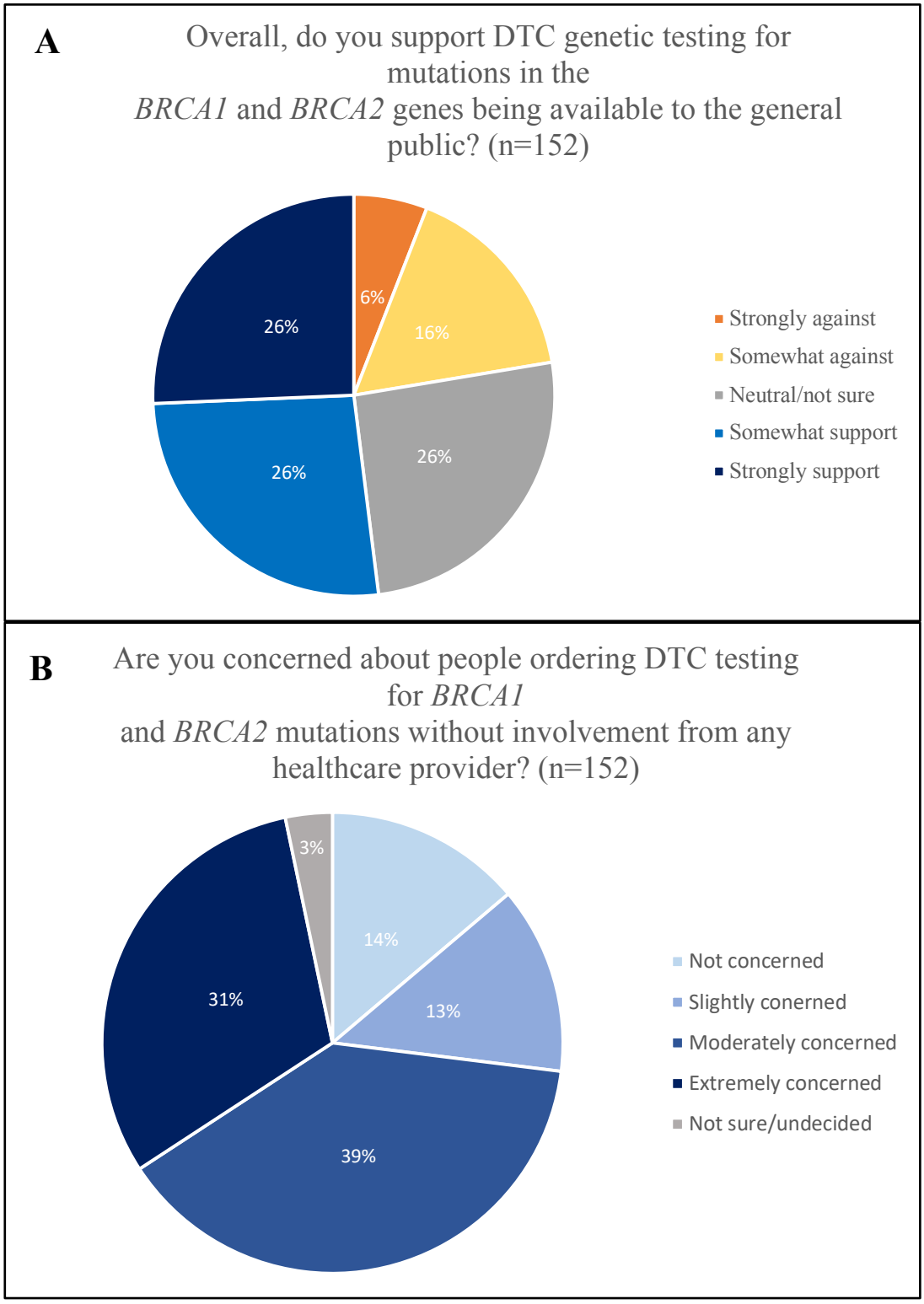

Figure 2.2 *BRCA1/2* carrier support (**A**) and concerns about (**B**) DTC-GT for *BRCA1/2* mutations

2.4.7 Thematic analysis

Within the questionnaire, we asked participants to elaborate on their responses to the questions about whether they overall support DTC-GT availability for *BRCA1/2* mutation testing and about whether they had concerns about DTC-GT for *BRCA1/2* mutations. Sixty-eight participants elaborated on their support/lack of support for DTC-GT and 66 participants elaborated on concerns they had. For both questions, themes were broken down into concerns regarding DTC-GT for *BRCA1/2* mutations and reasons for supporting DTC-GT for *BRCA1/2* mutations.

2.4.7.1 Concerns regarding DTC-GT for BRCA1/2 mutations

For both questions, accuracy and false negatives associated with the testing was a major concern with DTC-GT. When asked whether they support DTC-GT, 31 of the respondents (45.6%) cited accuracy and/or false negative concerns as a reason they may not support it. When asked specifically about their concerns regarding DTC-GT for *BRCA1/2* mutations, 21 respondents (31.8%) cited accuracy/false negative concerns.

"I believe the results are not accurate, misleading and dangerous"

"Too many false negatives, which gives a sense of security that is false and is risky"

Another theme that emerged was that participants were concerned about lack of healthcare provider guidance on how to handle a positive test result with DTC-GT. When asked to describe what their concerns were, 31 respondents (47%) said they were concerned about lack of involvement from a healthcare professional, either for psychosocial support or for answering questions about navigating next steps. Of these 31 respondents, 26 specifically cited that people may not understand clinical management

without a healthcare provider, and 12 cited a provider should be involved for psychosocial support (7 participants cited both concerns).

"*Counseling, explanations, questions answered in person and immediately as I heard result was so helpful. I would not have wanted to be alone with no other info"*

"*Finding out you have this mutation has created nothing but anxiety and depression. To tell someone they have this mutation or them finding out can be a shock and without some form of support can lead to severe depression*"

2.4.7.2 Reasons for supporting DTC-GT for BRCA1/2 mutations

Two main themes emerged for reasons to support *DTC-GT* for *BRCA1/2* mutations: increased accessibility and empowerment. Of the 68 respondents who elaborated on why they did or did not support DTC-GT for *BRCA1/2* mutations, 24 (35.3%) said they supported it because it increases accessibility to *BRCA1/2* testing, with 7 respondents (10.3%) specifically mentioning it would be a good option for those who cannot afford clinical testing.

"I believe everyone should be able to know what health mutations/risks exist for them. Saying they have to get it from a clinic will prevent many people from seeking the information"

Six participants commented that more people being able to learn their genetic status is a benefit that empowers patients to take action.

"It's important to get information in the hands of patients so they can take control of their health"

2.4.8 Correlations

No significant correlations were observed between satisfaction with any aspect of previous genetic testing experience and whether participants were overall in support or concerned about DTC-GT for *BRCA1/2* mutations. Multiple correlations were found between aspects of previous genetic testing experience and whether participants would have chosen DTC-GT or clinical testing for themselves (assuming accuracy was the same for each test). For previous genetic testing experience, time it took to get an appointment, ease of accessing a clinic, cost of testing, information provided on *BRCA1/2* genes and cancer, information provided on management for positive results, and risk estimation for family members were all significantly correlated with whether participants would have preferred DTC-GT or clinical testing for themselves. People who rated these aspects of their genetic testing more positively were more likely to have chosen clinical testing for themselves while those who rated these aspects of their own experience negatively were more likely to have chosen DTC-GT for themselves, with ease of accessing a clinic and risk assessment having the strongest significant correlations ($p=0.001$), followed by time to get an appointment ($p=0.012$) and cost of testing ($p=0.013$). Psychosocial support was the only factor related to previous genetic testing experience that was not significantly correlated with which form of testing participants would have chosen for themselves ($p=0.078$).

How participants viewed psychosocial support with DTC-GT was correlated with whether they supported DTC-GT for *BRCA1/2* mutations and with whether they had concerns with DTC-GT for *BRCA1/2* mutations. A lower rating of psychosocial support provided with DTC-GT was correlated with less support of its availability ($p=<0.001$)

and more concerns (p= 0.007). Additionally, there was a positive correlation between participant age and level of concern about DTC-GT for *BRCA1/2* mutations (p=0.04).

2.5 Discussion

This study aimed to elucidate the attitudes of *BRCA1/2* mutation carriers toward DTC-GT of the *BRCA1* and *BRCA2* genes. In surveying *BRCA1/2* carriers who were diagnosed via clinical genetic testing, we found that most participants supported the general availability of DTC-GT for *BRCA1/2* mutations, in particular because it improves accessibility to this important information. However, most participants also had concerns related to the accuracy of DTG-GT and the availability of clinical and psychological support for mutation-positive patients.

We anticipated that most *BRCA1/2* carriers would support DTC-GT for *BRCA1/2* mutations, and not surprisingly, the most commonly cited reason in support of DTC-GT was improved access to testing. Specifically, multiple participants noted that DTC-GT might be a good option for women who desired testing but experienced barriers (such as financial difficulties) to accessing clinical genetic testing. In general, participants rated the accessibility of DTC-GT superior to the accessibility of clinical testing, and those participants who rated accessibility-related aspects (e.g., ease of accessing a clinic or cost of testing) of their previous genetic testing experience more negatively were more likely to prefer DTC-GT for themselves if given the choice again. This aligns with previous research that has shown that consumers of DTC-GT strongly support the increased accessibility of genetic testing that DTC-GT offers (Gollust et al., 2017). Even genetics professionals agree that DTC-GT could be a viable option for patients who want genetic testing but have limited accessibility to clinical testing. In one study, 90% of genetic

counselors surveyed said they would definitely or possibly consider referring a patient to DTC-GT if that patient had limited access clinical testing due to where they live, and over 70% of genetic counselors said they would consider referring patients to a DTC-GT company if they had concerns over privacy or genetic discrimination (Hock et al., 2011). Additionally, previous research has shown that most women who are at high risk of developing breast and/or ovarian cancer are in favor of direct-to-consumer *advertising* for *BRCA1/2* genetic testing, asserting that direct-to-consumer advertising may be a good way of helping women be informed about potential genetic risks for breast and ovarian cancer and allowing them to take action by speaking to their healthcare provider (Perez et al., 2011). Multiple participants in our study also highlighted DTC-GT could lead to increased patient empowerment.

Historically, surveys have suggested that people affected with genetic conditions or at-risk for genetic conditions are generally not in favor of DTC-GT. In a 2011 study, only 20% of women who were at high risk for breast and/or ovarian cancer surveyed said that they thought online access to genetic testing for *BRCA1/2* gene mutations was a good idea (Perez et al., 2011). A survey of cystic fibrosis patients and parents of patients found that they were generally skeptical of DTC-GT for cystic fibrosis carrier status and the majority believed that a healthcare provider should be involved (Janssens et al., 2015). Our finding that the majority of *BRCA1/2* carriers surveyed were in favor of DTC-GT for *BRCA1/2* mutations differs from these previous findings. One reason may be that over the past few years, our society has become increasingly more accepting and trusting of technology and internet-based companies (Rainie & Anderson, 2017). Additionally, many women supported DTC-GT in this study because it was an option for people who

had limited accessibility to clinical testing. When asked what they would prefer for themselves, most women in our study indicated they still would prefer clinical testing over DTC-GT. Overall, it seems that while these women generally see clinical genetic testing for *BRCA1/2* mutations as superior to DTC-GT as has been found in previous studies, they believe DTC-GT should be available for those who may not have easy access to clinical testing.

While participants were generally not opposed to the *availability* of DTC-GT for *BRCA1/2* mutations, they also indicated that they had concerns with DTC-GT for these mutations. The majority also indicated that they still would have pursued clinical testing over DTC-GT if given a choice between the two options. The most frequent concern was accuracy of DTC-GT and false negatives. Currently, the DTC-GT for *BRCA1/2* being offered via 23andMe only reports on three total mutations out of thousands of known mutations in these genes. This means that the vast majority of true *BRCA1/2* mutation carriers tested through 23andMe will receive a negative *BRCA1/2* report. While we did not explicitly tell participants this information within our questionnaire, many cited this limitation of the test in the free response portion of the questionnaire. When presented with a scenario in our survey where DTC-GT detects 15% of *BRCA1/2* mutations while clinical testing detects 95%, only 4 out of 150 respondents indicated they would likely choose DTC-GT over clinical testing. Taken together with the responses to the open-ended questions, this indicates that patients would strongly prefer the test that has a higher detection rate if given the opportunity to choose, and that participants are worried about false reassurance in those patients who do not understand the limitations of a negative result with DTC-GT.

Participants were also concerned about limited information and support for those who have positive results. Similar concerns have been raised by both consumers and healthcare professionals in the past. There have been reports of people learning that they were *BRCA1/2* mutation carriers via DTC-GT and having a significant negative reaction, including a case report where a woman experienced psychological distress and difficulty comprehending her positive result (Dohany et al., 2012) and a participant in another study stating that learning he carried a BRCA mutation via DTC-GT caused him emotional distress (Francke et al., 2013). Additionally, multiple respondents in our study commented that they desired psychological support and needed a clinician to answer questions when learning their own result. However, the limited research done on this topic has shown that most people who learned of their *BRCA1/2* mutation via DTC-GT did not report having extreme negative reactions to learning their result, and the majority also brought their results to discuss and review with a healthcare provider (Francke et al., 2013), suggesting that while risks of learning about *BRCA1/2* carrier status via DTC-GT may be present, they may not be as prevalent as some believe.

Increased accessibility to genetic testing via DTC-GT may be particularly relevant when testing for *BRCA1/2* mutations. Often, clinical genetic testing for *BRCA1/2* will not be covered by insurance unless the patient meets specific criteria set by insurers, even when the clinician feels they could benefit from testing. In other cases, clinicians may not recognize patients who may benefit from testing due to small family size or limited family history information. Indeed, previous research has shown that as many as half of women found to be *BRCA1/2* mutation carriers post-cancer-diagnosis did not meet testing criteria prior to their own diagnosis (Weitzel et al., 2007). Therefore, the availability of

DTC-GT for *BRCA1/2* mutations has the potential to identify carriers that may have been missed in a clinical setting due to lack of insurance coverage or if they have limited personal and family histories of cancer.

Due to the small sample size of this study, and the inability to adjust for confounding via multivariable analyses, we were limited to exploratory analyses of the correlations between variables. Nonetheless, our data suggest some future avenues of investigation that may be worthwhile to pursue. For example, we found no significant correlations between any aspect of participants' previous genetic testing experience and whether they were in support of DTC-GT; there were significant correlations between how women rated psychological support with DTC-GT and whether they overall supported it and had concerns about it. Those who rated psychological support lower in DTC-GT were less likely to support it and had more concerns. It is well-established that psychological support is an important part of the genetic counseling process of women who receive a positive *BRCA1/2* result (i.e. Lieberman et al., 2017), so it is not surprising that women who have experienced the psychological challenges that come with a positive result may be less supportive of a testing model that offers less psychological support. Age was also positively correlated with level of concern about DTC-GT for *BRCA1/2* mutations. This may be due to older individuals having more negative attitudes towards new technologies (Hauk, Hüffmeier & Krumm, 2018). These associations warrant further investigation.

2.5.1 Limitations

Although our survey was open to both men and women, only 3 men qualified for our study and began the questionnaire compared to 181 women. There are a few possible

explanations for this significant discrepancy in the sex of the participants. One reason is that women are more likely to undergo genetic testing *BRCA1/2* mutations and therefore be identified as carriers (Daly, 2009). Additionally, research shows that women tend to be more engaged in their healthcare (i.e. Etingen et al., 2018) and are more likely to participate in support groups than men (Krizek et al., 1999; Lieberman, 2008) which is where most of our participants were recruited from. A future survey of male carriers would be needed to determine if men hold similar attitudes towards DTC-GT for *BRCA1/2* mutations.

While our study was open to people of all ethnic backgrounds, we did not have any participants in our study who identify as African-American or black. There are a few potential reasons for this. One reason is that the results of genetic testing vary based on ethnicity. For example, about 5-6% of people of Caucasian ancestry get a variant of unknown significance as a result, while that number can be as high as 21% in African-Americans (Ready et al., 2011). Additionally, it has been well-established that African-Americans tend to have less access to specialty healthcare providers compared to the Caucasian population and are less likely to pursue genetic testing than the Caucasian population (Forman & Hall, 2009). Future recruitment from African-American and other minority-focused support groups or patient communities could help to reach these groups. The current dataset does not permit us to investigate similarities and differences in attitudes towards DTC-GT across ethnic groups.

Participants for this study were recruited from support groups made specifically for people who have a strong genetic predisposition for breast and ovarian cancer. This is only a small proportion of *BRCA1/2* mutation carriers and, as mentioned previously, is

not accurately representative as the entire *BRCA1/2* mutation carrier population. Therefore, our results may not be generalizable to the *BRCA1/2* mutation carrier population as a whole, especially males and people of ethnicities other than Caucasian.

2.5.2 Future Research

To make the results of this research more generalizable, further research could be conducted with a more diverse group of participants, including additional participants of different ethnic backgrounds, socio-economic status, and males. Recruiting mutation-positive participants outside of support groups, such as directly through a genetics clinic or high-risk breast cancer clinic, would provide a less-biased sample of participants. Additionally, further research could be done gathering the thoughts and perspectives of people who went through genetic counseling and genetic testing for *BRCA1/2* mutations and tested negative, as undergoing the clinical genetic testing process and receiving a negative result entails a set of psychosocial and genetic counseling challenges that are different from those patients who receive a positive result. Understanding the limitations of testing and residual risk that accompany a negative result are an important part of the clinical genetic testing process and it would be interesting to see how this population of patients feel about DTC-GT for *BRCA1/2* mutations, especially since most patients who do undergo genetic testing for hereditary cancer predisposition syndromes receive a negative result (LaDuca et al., 2014; Couch et al., 2017).

2.5.3 Conclusions & Practice Implications

This study is the first to our knowledge with the primary goal of investigating the perspectives of *BRCA1/2* mutation carriers on DTC-GT for *BRCA1/2* mutations. Overall, our study shows that even among those patients who would be most aware of the

potential utility of clinical genetic testing (i.e., those who received a diagnosis through testing), there was support for the availability of DTC-GT. Because participants' concerns were largely limited to the those surrounding accuracy and availability of adequate counselling and follow-up support, it may be that an enhanced DTC-GT model which incorporates pre- and/or post-test counseling by a certified genetic counselor could be a viable option that would have support from the BRCA-mutation carrier population. Participants believed that the accessibility of DTC-GT is beneficial to those who may not have access to genetic testing otherwise. In fact, women surveyed were more likely to indicate they would have chosen DTC-GT for themselves if cost of clinical testing was significantly higher, the drive to a clinic was far, or there was a long wait for an appointment. Further, negative experiences with cost and clinic accessibility with their own clinical testing were correlated with preference for DTC-GT if they were to get tested again. These findings suggest that potential *BRCA1/2* carriers may be willing to sacrifice the genetic counseling offered through clinical testing in favor of easy accessibility, highlighting the need to focus on expanding accessibility of clinical genetic testing to a broader population.

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APPENDIX A

WEB-BASED QUESTIONNAIRE

Hello,

Thank you for your interest in our study. You are being asked to participate in our study because you are a carrier of a *BRCA1* or *BRCA2* mutation that was identified through clinical genetic testing. Your participation in this study is voluntary and you can choose to leave the study at any time. You can choose to skip (not answer) individual questions in the survey. Your answers will be anonymous (your responses cannot be linked to your personal identity) and confidential (your responses will be stored securely, and only accessible to members of the research team conducting the study). By completing this survey, you are consenting to its use in this study and any future research, presentations, or publications. However, you may withdraw your consent at any time by contacting the individuals listed below. The risks of participating in this study are minimal: you may experience negative emotions when recalling your genetic testing experience. There is no direct personal benefit to participating in this study; however, your input may contribute to improved understanding of patient preferences for genetic counseling and direct-to-consumer access to genetic testing.

The online questionnaire should take about 10-15 minutes to complete. Each participant who completes the survey has the option to be entered in a drawing to win a $10 Amazon gift card. One drawing will take place for the gift card at the completion of data collection. If you wish to enter the drawing, a link will be given at the end of the questionnaire where you can provide your email to enter the drawing without connecting your email address to your previous answers. The winner of the drawing will be notified via email in February 2019.

If you have any questions, please do not hesitate to contact me by email at caitlyn.mitchell@uscmed.sc.edu or my advisor, Alexis Carere, ScD, CGC at alexis.carere@lhsc.on.ca. Additionally, please contact myself or my advisor via email if you wish to receive the results of the survey once it is complete.

Sincerely,
Caitlyn Mitchell, MS
Genetic Counseling Student
University of South Carolina

Page 1: Eligibility

1. Have you tested positive for a mutation in *BRCA1* or *BRCA2*?

a. Yes [*continue to next page*]
b. No [*exit survey to "thank you" page*]

Page 2: Eligibility

2. Were you the first person in your family found to have this mutation?
    a. Yes [*continue to next page*]
    b. No [*exit survey to "thank you" page*]

Page 3: Eligibility

3. Did you receive genetic testing through a cancer clinic or genetics clinic, where a genetic counselor, oncologist, or other physician or health care provider ordered the test? (Note: if you learned of your mutation via a direct-to-consumer testing company, such as 23andMe or Color Genomics, please answer "No")
    a. Yes [*continue to next section*]
    b. No [*exit survey to "thank you" page*]

Page 4: Demographic Information

1. What is your gender?
    i) Male
    ii) Female
    iii) Prefer not to answer

2. What is your age? [blank box for age]

3. How old were you when you tested positive for a *BRCA1* or *BRCA2* mutation? (approximate if unsure) [blank box for age]

4. What is your race? (Select all that apply)
    i) Alaska Native
    ii) American Indian
    iii) Asian
    iv) African American
    v) Caucasian
    vi) Hispanic
    vii) Native American
    viii) Native Hawaiian/Pacific Islander
    ix) Unknown
    x) Other
    xi) Do not wish to specify

5. Do you reside in the United States?
    i) Yes
    ii) No

6. What is your highest level of education
   i) High school
   ii) Some college education
   iii) College degree
   iv) Some graduate school
   v) Doctoral/Professional degree

7. What is your annual household income?
   i) <$40,000
   ii) $40,000-$99,999
   iii) $100,000- $199,999
   iv) >$200,000
   v) Prefer not to say

8. Do you have children?
   i) Yes
   ii) No

9. Do you have health insurance?
   i) Yes
   ii) No

Page 5: Genetic testing experience

10. Who ordered your cancer genetic testing?
    a. Oncologist
    b. Genetic counselor
    c. Obstetrician or gynecologist
    d. Family practitioner (family doctor or family nurse practitioner)
    e. Advanced practice nurse in genetics (APNG)
    f. Other (please specify): _____

11. How were you referred for genetic testing?
    a. Referred by doctor or other healthcare provider after personal history of cancer
    b. Referred by doctor or other healthcare provider due to family history of cancer
    c. Referred by doctor for another reason
    d. Sought genetic counseling on my own due to personal history of cancer
    e. Sought genetic counseling on my own due to family history of cancer
    f. Sought genetic counseling on my own for another reason

12. What type of testing was ordered for you?
    a. *BRCA1* and *BRCA2* genes only
    b. A panel (large number) of genes, including more than *BRCA1* and *BRCA2*
    c. I don't remember

13. To what extent was your testing covered by insurance?
    a. Fully covered
    b. Partially covered (i.e. I had to pay a co-pay)
    c. Not covered at all, paid out-of-pocket

14. How long did you wait for results?
    a. Less than 1 week
    b. Between 1 and 2 weeks
    c. Between 2 and 4 weeks
    d. Between 4 and 8 weeks
    e. Over 8 weeks

Page 6: Genetic testing information (continued)

15. Overall, how satisfied were you with your genetic testing experience?
    1- Very unsatisfied
    2- Somewhat unsatisfied
    3- Neutral
    4- Somewhat satisfied
    5- Very satisfied

16. Please rate the following aspects of your genetic counseling or genetic testing experience on a scale of 1 (Very negative) to 5 (Very positive)

	1 Very Negative	**2**	**3 Neutral**	**4**	**5 Very positive**
Time to get an appointment	□	□	□	□	□
Ease of accessing a clinic	□	□	□	□	□
Cost of testing	□	□	□	□	□
Risk assessment (provider determining your likelihood of having a mutation)	□	□	□	□	□
Information provided on *BRCA1* and *BRCA2* genes and breast cancer	□	□	□	□	□
Psychological support	□	□	□	□	□
Information provided on management/treatment for mutation positive patients	□	□	□	□	□
Risk estimation for other family members	□	□	□	□	□

17. Thinking back to when you received the results of your genetic testing, were you:

	1 Not at all	2	3 Moderately	4	5 Extremely
Surprised?	□	□	□	□	□
Upset?	□	□	□	□	□
Relieved?	□	□	□	□	□

18. What actions did you take after you received your genetic testing results? Select all that apply.
    1. No action taken
    2. Increased screening (mammograms, MRI, clinical exams, self-exams)
    3. Communication of results to family members
    4. Changing cancer treatment plan
    5. Prophylactic surgery (mastectomy and/or salpingo-oophorectomy)
    6. Other: _____

Page 7- DTC testing

In contrast to the traditional clinical testing experience, direct-to-consumer (DTC) genetic testing refers to genetic testing that consumers can order from home, in many cases without involvement from healthcare providers or insurance companies. These tests allow consumers to access their own genetic information and learn more about their genetic predisposition to certain traits and disease. Typically, consumers order DTC genetic testing online or via telephone for a cost ranging from $99-250. A kit is then mailed to the customer's house, containing a container to collect saliva. The saliva sample is then mailed back to the company. The customer's results will be reported back to them in the form of an online report. The report typically provides an interpretation of what their genetic results mean for their health and susceptibility to disease. Historically, DTC testing has been utilized to provide information about ancestry, disease risk (such as heart disease or Parkinson's disease), and carrier status for recessive genetic conditions such as cystic fibrosis. More recently, the FDA has approved some companies to provide DTC testing for cancer-related genes, such as *BRCA1* and *BRCA2*. This allows any person over the age of 18 to order genetic testing for *BRCA1* and *BRCA2* mutations from anywhere in the country at any time, without having to involve a physician or other healthcare provider. No referral or appointment is necessary to undergo DTC-genetic testing for *BRCA1* and *BRCA2* mutations, and once results are available, the costumer can access them any time.

Pre- and post-test genetic counseling is usually not included as part of the DTC genetic testing experience. Those customers who wish to review their results with a clinician, ask questions, or get referrals to other specialists must make those arrangements on their own, and typically pay for the genetic counseling out-of-pocket.

In our study, we are interested in understanding the perspectives of *BRCA1* and *BRCA2* mutation carriers who underwent the clinical testing experience through a

physician or genetic counselor. We are interested in learning how you perceive direct-to-consumer genetic testing for *BRCA1* and *BRCA2* mutations.

19. Prior to reading the description above, had you heard of direct-to-consumer (DTC) genetic testing?
    i) Yes, I had heard of DTC genetic testing and I knew what the term meant
    ii) Yes, I had heard of DTC genetic testing, but I did not know what the term meant
    iii) No, I had not heard of DTC genetic testing prior to this survey

20. Have you had DTC genetic testing before (such as 23andMe, Ancestry DNA)?
    i) Yes
    ii) No

21. Thinking about both DTC genetic testing and clinical genetic testing, if both options had been equally accessible to you at the time you were considering *BRCA1* and *BRCA2* mutation testing, which option would you have preferred? For the purposes of this question, please assume that the accuracy of the genetic test is the same whether ordered clinically or through a DTC genetic testing company.
    1- Definitely clinical testing
    2- Probably clinical testing
    3- Not sure
    4- Probably DTC testing
    5- Definitely DTC testing

Please explain why you chose this answer

22. Which aspects of DTC genetic testing do you see favorably compared to clinical genetic testing? Please rate on a scale of 1 (very unfavorable) to 5 (very favorable).

	1 Very unfavorable compared to clinical	**2**	**3 Same as clinical**	**4**	**5 Very favorable compared to clinical**
Cost of DTC testing	□	□	□	□	□
Accessibility of DTC testing	□	□	□	□	□
Time of DTC testing	□	□	□	□	□
Information/education provided in DTC testing	□	□	□	□	□
Psychosocial support in DTC testing	□	□	□	□	□

Page 8 – Scenarios
Please think back to your own genetic testing experience when answering the following questions.

For the purposes of questions 1 through 4 below, please assume that the accuracy of the genetic test is the same whether ordered clinically or through a DTC-GT company.

23. If there had been a 2+ month wait to schedule a clinical genetic testing appointment, or you could have ordered DTC testing online immediately, which would you have preferred?

1- Definitely clinical testing
2- Probably clinical testing
3- Not sure
4- Probably DTC testing
5- Definitely DTC testing

Please explain why you chose this answer

24. If you had to pay out-of-pocket for clinical genetic testing for *BRCA1* and *BRCA2* mutations ($250-400), or you could have ordered DTC *BRCA1* and *BRCA2* testing for $99, which would you have preferred?

1- Definitely clinical testing
2- Probably clinical testing
3- Not sure
4- Probably DTC testing
5- Definitely DTC testing

Please explain why you chose this answer

25. If the nearest available clinic for *BRCA1* and *BRCA2* testing was a 2-hour drive, would you choose to get tested in this clinic, or order DTC testing?

1- Definitely clinical testing
2- Probably clinical testing
3- Not sure
4- Probably DTC testing
5- Definitely DTC testing

Please explain why you chose this answer

26. If your children desired DTC testing rather than clinical testing to see if they have your *BRCA1* or *BRCA2* mutation, would you support their decision?

1- Definitely would not support
2- Probably would not support
3- Neutral
4- Probably support
5- Definitely support

Please explain why you chose this answer

27. For this question, imagine that **DTC genetic testing** of *BRCA1* and *BRCA2* can detect mutations in 15% of individuals with a mutation. In other words, of 100 true mutation carriers, 15 will receive a positive genetic testing result, while 85 will receive an incorrect, negative result (a "false negative"). However, this testing would be widely available to all interested individuals, and has the potential to detect mutations in people who otherwise would not meet clinical testing criteria (e.g., they haven't had cancer themselves, or do not have a significant family history of cancer).

Also imagine that **clinical genetic testing** of *BRCA1* and *BRCA2* can detect mutations in 95% of individuals with a mutation. In other words, of 100 true mutation carriers, 95 will receive a positive genetic testing result, while 5 will receive an incorrect, "false negative" result. However, this testing is limited to those individuals who meet certain criteria (e.g., have had early onset breast or ovarian cancer, or have a significant family history of cancer); therefore, some people with mutations will never be tested and their mutations would not be detected.

In this situation, if you could choose either DTC genetic testing or clinical genetic testing for yourself, which option would you have chosen?

1- Definitely clinical testing
2- Probably clinical testing
3- Not sure
4- Probably DTC testing
5- Definitely DTC testing

Please explain why you chose this answer

28. Now imagine you have a friend who is concerned about her risk of breast cancer. She could order DTC-GT, or she could ask her doctor for a referral for clinical genetic testing. If she orders DTC-GT, she will definitely get testing, but it will only detect 15% of mutations. If she is referred to a clinic, she may not be offered genetic testing (depending on whether or not she meets criteria), but if she is found to meet high-risk criteria, then she would be offered testing that detects 95% of mutations. In this situation, which type of testing would you recommend to your friend?

1- Definitely clinical testing
2- Probably clinical testing
3- Not sure
4- Probably DTC testing
5- Definitely DTC testing

Please explain why you chose this answer

Page 9- Final questions

29. Overall, do you support DTC genetic testing for mutations in the *BRCA1* and *BRCA2* genes being available to the general public?
    1- Strongly against
    2- Somewhat against
    3- Neutral/not sure
    4- Somewhat support
    5- Strongly support

Please explain why you chose this answer

30. Are you concerned about people ordering DTC testing for *BRCA1* and *BRCA2* mutations without involvement from any healthcare provider?
    1- Not concerned
    2- Slightly concerned
    3- Very concerned
    4- Extremely concerned
    5- Not sure/undecided

If you have concerns, please briefly describe them. If you do not have any concerns, please explain why.