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## Genetic Counselors' Approaches to Direct-to-Consumer Genetic Testing for Hereditary Breast Cancer

Sarah Burke

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GENETIC COUNSELORS' APPROACHES TO DIRECT-TO-  
CONSUMER GENETIC TESTING FOR HEREDITARY BREAST CANCER

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CONSUMER GENETIC TESTING FOR HEREDITARY BREAST CANCER

A

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# GENETIC COUNSELORS' APPROACHES TO DIRECT-TO- CONSUMER GENETIC TESTING FOR HEREDITARY BREAST CANCER

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## ABSTRACT

Given the increasing availability of health-related direct-to-consumer genetic testing (DTC-GT) and third-party interpretation (TPI) services, it is likely that genetic counselors (GCs) will continue to encounter consumers that require follow-up counseling for their results. The National Comprehensive Cancer Network recommends clinical-grade genetic testing to confirm commercial results; however, the type of testing that GCs select remains uncharacterized. Therefore, we aimed to describe the specific recommendations that cancer GCs make for confirmatory genetic testing in probands who have already obtained DTC-GT results or TPI data that reported a *BRCA1/2* pathogenic variant. We recruited 80 GCs specializing in hereditary cancer and administered a survey that assessed their testing strategy for probands from three hypothetical case scenarios with variable personal and family histories of cancer. The majority of participants would recommend confirmatory clinical-grade genetic testing for both probands' DTC-GT results and TPI data (77/80, 96%). For probands with a personal diagnosis of breast cancer and a DTC-GT result for an Ashkenazi Jewish *BRCA1/2* founder mutation, participants were more likely to recommend targeted testing (single-site or comprehensive *BRCA1/2* analysis) (30/77, 39%,  $p < 0.01$ ). In scenarios where probands had DTC-GT results but lacked a personal and/or family history suggestive of hereditary cancer, and in all scenarios where the probands had positive TPI data for a *BRCA1/2* variant, most

GCs would recommend a multi-gene panel. Our results show that GCs are unified in their practice of recommending confirmatory genetic testing, although the selected clinical-grade test varies depending on the proband's cancer history and type of commercial testing they obtained. As the market for DTC-GT expands and this patient population continues to grow, genetic counselors must continue to be knowledgeable on this topic.

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## INTRODUCTION

Direct-to-consumer genetic testing (DTC-GT) has fundamentally changed the way that individuals can obtain personal genetic information, which may include predictions about their health. The DTC-GT company 23andMe issues personalized health reports for various multifactorial conditions and single-gene disorders. Many DTC-GT companies also provide the option to download raw genotype data. It is estimated that as many as 60% of consumers would be interested in utilizing online third-party interpretation (TPI) services to further analyze their raw data to obtain additional health information not included in their original DTC-GT report (Wang et al., 2018).

An important concern from healthcare providers related to DTC-GT is the methodology of this testing. Whereas clinical diagnostic testing is ordered as part of a medical evaluation and typically includes comprehensive full-gene sequencing with deletion and duplication analyses, DTC-GT utilizes genotyping of common single nucleotide polymorphisms (SNPs) to provide information to generally healthy individuals (Carere et al., 2015). 23andMe offers testing for hereditary breast and ovarian cancer (HBOC) syndrome, but only includes genotyping of the three Ashkenazi Jewish (AJ) founder mutations. This limitation may create false reassurance for consumers with negative results as there are thousands of disease-causing *BRCA1/2* variants not assessed by this test (Horton et al., 2019). Further, TPI services function by cross-referencing raw genotype data with public databases, such as SNPedia wiki, to provide classifications on the reported variants. However, the majority of classifications in some databases may be incorrect (Badalato et al., 2017; Dorschner 2013; Moscarello, Murray, Reuter, & Demo, 2019; Wang et al., 2017). The misclassification of such variants contributes to Tandy-Connor et al.'s (2018) finding that as many as 40% of the reported variants from TPI data are false positives. For these reasons, the

National Comprehensive Cancer Network (NCCN) recommends confirmatory germline testing through an appropriately certified clinical-grade laboratory when potentially pathogenic variants are identified by commercial entities (NCCN, 2020). Other concerns related to these services include an inadequate informed consent process, questionable clinical validity and utility, and potential misuse of false positive results (Badalato, Kalokairinou, & Borry, 2017; Horton et al., 2019).

Despite these considerations, the DTC-GT delivery model has become increasingly accessible. More than 14 million people have utilized DTC-GT, and that figure is expected to reach 100 million by 2021 (Khan & Mittelman, 2018). The majority of DTC-GT companies recommend discussion of results with a healthcare provider (Singleton et al., 2012), and approximately one-third of this large consumer base will share their report with a provider (Bloss et al., 2013; Wang et al., 2018). In an effort to understand which practitioners most frequently encounter DTC-GT results, Van der Wouden et al. (2012) reported that the majority of consumers planned to share their health-related results with their primary care physician (PCP). However, most PCPs reported a lack of knowledge regarding DTC-GT reports (Carroll et al., 2016; Powell et al., 2012). In contrast, genetic counselors (GCs) undergo extensive training to explain the potential implications of genetic test results, including medical management, screening, preventative care, and how family members may be affected (Ramos & Weissman, 2018); however, no study to date has surveyed GCs' perceived comfort level regarding counseling patients on DTC-GT reports. Nonetheless, given their training and skillset, GCs may be the most capable provider to bridge the gap between patients and their DTC-GT result and/or TPI data. Thus, the National Society of Genetic Counselors (NSGC) advises consumers interested in learning additional information about their individualized health-related risks to consult with a GC (NSGC, 2018).

Despite this recommendation from NSGC, it remains unknown how GCs are incorporating DTC-GT results and TPI data into their clinical practice. The field of hereditary breast cancer is well-suited to further study of this topic. Testing for HBOC syndrome is widely available through DTC-GT companies, the majority of TPI data false-positives occur in *BRCA1/2* (Tandy-Connor et al., 2018), and there are implications for actionable medical management once affected individuals are identified. The purpose of this study is to describe what recommendations, if any, GCs make for clinical-grade genetic testing in patients who have already obtained DTC-GT results or TPI data that reported a *BRCA1/2* pathogenic variant in order to help inform counseling approaches and consensus for this expanding group of patients.

## METHODS

### Participants

This study was approved by the institutional review board at the University of Texas Health Science Center at Houston (HSC-GEN-19-0445). Participants were recruited via an email that contained a survey link distributed to all members of NSGC in the United States and Canada. Eligible participants included practicing GCs reporting clinical cancer genetics as their primary specialty, defined as greater than 50% of their time. Responses were collected from August to November 2019.

### Instrumentation

This study employed a cross-sectional design with an anonymous survey that was created using Qualtrics software (v. July 2019. Qualtrics, Provo, UT). Survey questions were created by the authors and a formal validated measure was not used given the unique aims of this study. Participants were asked about demographic information, experience with DTC-GT results and TPI data in clinic, and three hypothetical case scenarios. They were also given

Likert scales to assess perceived challenges associated with counseling about DTC-GT and desired resources to aid their counseling of these patients.

### **Data Analysis**

STATA statistical software (version 13.1) was utilized for data analysis and statistical significance was assumed at a Type I error rate of 5% ( $p < 0.05$ ). Frequencies were reported for demographic variables. A Friedman's test with post-hoc analysis was applied to assess for statistically significant differences in the distribution of the type of genetic testing recommended between the three sub-scenarios for each individual pedigree (see Results section). Two comparisons were reported for each pedigree: no prior genetic testing compared to DTC-GT result, and no prior genetic testing compared to TPI data. For each comparison, only the participants that recommended genetic testing between both conditions were included.

## **RESULTS**

Of the 1,140 NSGC members eligible to participate, 108 surveys were submitted, yielding a response rate of 9.5%. Incomplete surveys were excluded, leaving 80 full responses available for analysis and an overall response rate of 7%. The majority of respondents were female (75/80, 94%), non-Hispanic Caucasians (72/80, 90%) and employed in university medical centers (42/80, 53%). There was variability within the region they practiced, the length of time they have been employed as GCs (IQR 1-5 years), and the proportion of breast cancer-related indications seen (IQR 50-72%). The demographics of our cohort are consistent with respondents to the 2019 NSGC Professional Status Survey, with the exception that GCs practicing in university medical centers were overrepresented in our sample. Of note, none of our participants indicated that they are employed at DTC-GT companies. Full demographic information is reported in Table 1.

**Table 1.** Demographics of participants ( $n = 80$ )

	$n$ (%)
Gender ( $n = 80$ )	
Female	75 (94)
Male	5 (6)
Race ( $n = 80$ )	
Caucasian	72 (90)
Asian	3 (4)
African American	1 (2)
Other	4 (4)
NSGC Region* ( $n = 80$ )	
Region 1 (Northeast)	5 (6)
Region 2 (Mid-Atlantic)	11 (14)
Region 3 (Southeast)	8 (10)
Region 4 (Midwest)	26 (32)
Region 5 (Southwest)	20 (25)
Region 6 (Pacific)	10 (13)
Institution Type ( $n = 80$ )	
University medical center	42 (53)
Private hospital	18 (22)
Public hospital	15 (19)
Physician's private office	2 (4)
Health maintenance org.	1 (2)
Number of years practicing in cancer genetics ( $n = 80$ )	
< 1	15 (19)
1 to 3	32 (40)
4-6	19 (24)
7-9	6 (7)
$\geq 10$	8 (10)
Proportion of breast-related indications seen ( $n = 72$ )	
0%	2 (3)
1-25%	4 (6)
26-50%	17 (24)
51-75%	37 (51)
79-100%	12 (16)

\* NSGC Regions:

Region 1: CT, MA, ME, NH, RI, VT, CN, Maritime Provinces

Region 2: DC, DE, MD, NJ, NY, PA, VA, WV, PR, VI, Quebec

Region 3: AL, FL, GA, KY, LA, MS, NC, SC, TN

Region 4: AR, IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, OK, SD, WI, Ontario

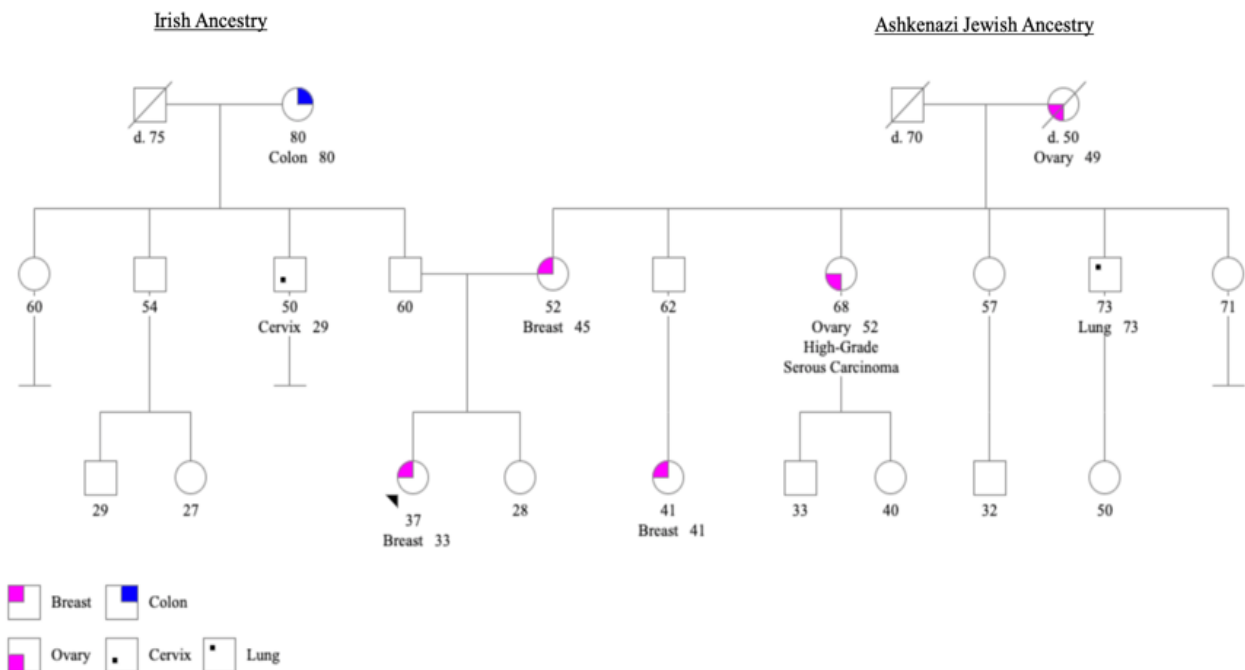
Region 5: AZ, CO, MT, NM, TX, UT, WY, Alberta, Manitoba, Sask.

Region 6: AK, CA, HI, ID, NV, OR, WA, British Columbia, Yukon

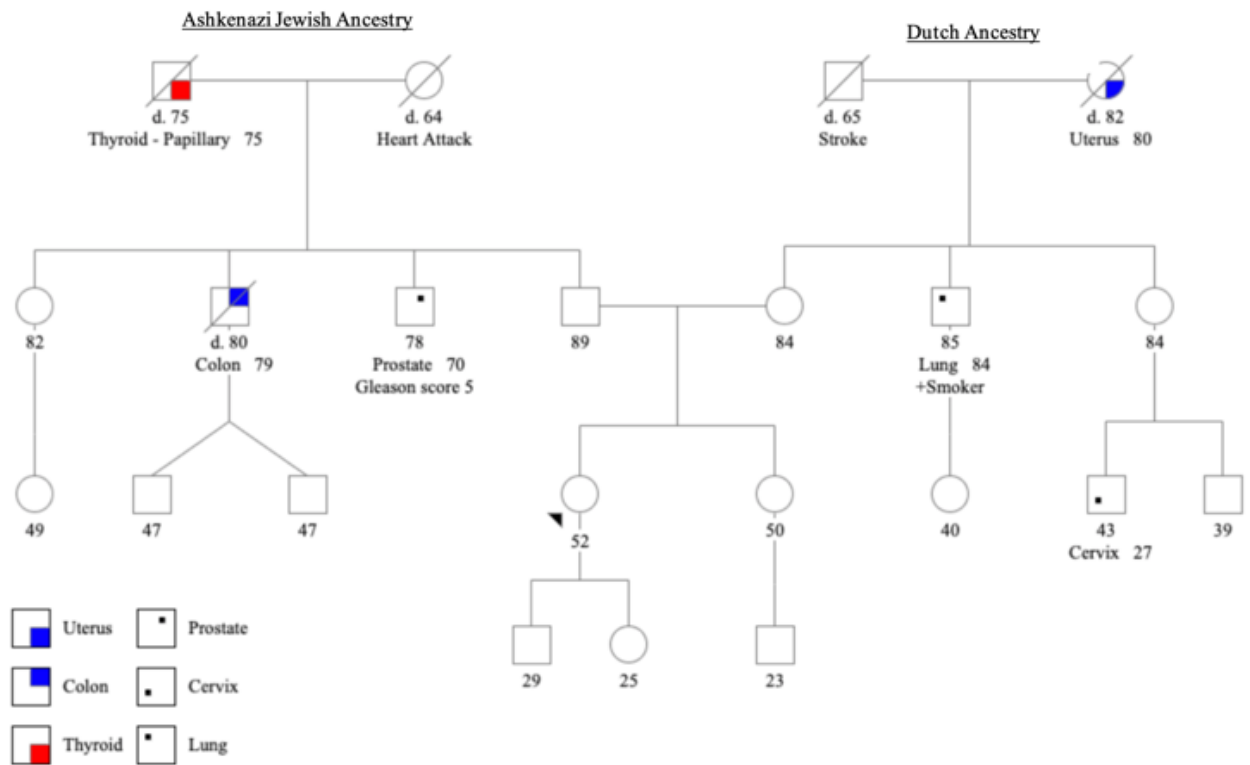
Overall, the majority of participating GCs reported that they have encountered health-related DTC-GT results in clinic. Specifically, 94% (75/80) have encountered health-related 23andMe results and 69% (55/80) have encountered health-related TPI data. Within the last year, participants reported providing counseling for a median of three 23andMe results (IQR 2-5) and two reports of TPI data (IQR 1-3). Slightly more than half (46/80, 58%) of GCs indicated that they have had discussions with other GCs and physicians in their clinic regarding how to address patients' DTC-GT results in attempts to establish a consensus within their clinic. In addition, 58% (46/80) indicated that they received information regarding DTC-GT counseling in their graduate school training.

**Figure 1.** Scenario pedigrees (a-c)

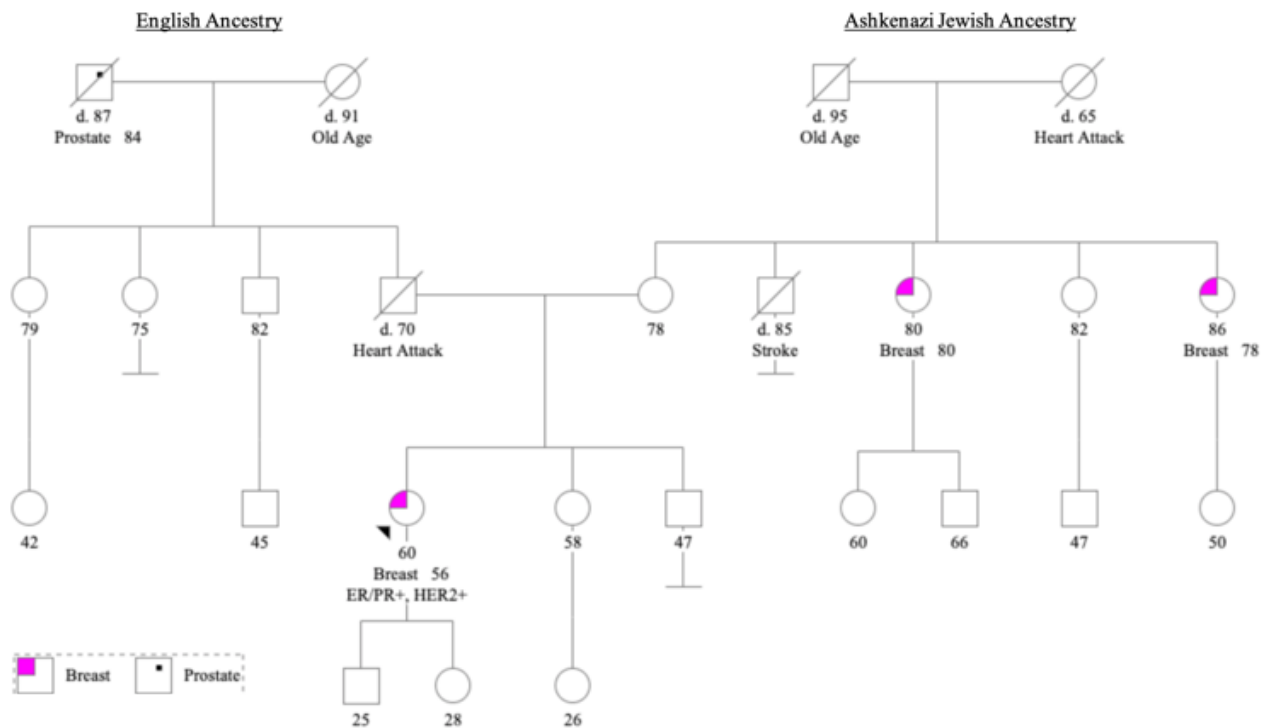
a) Scenario 1



b) Scenario 2



c) Scenario 3





## Scenario-Based Questions for Confirmatory Genetic Testing Recommendations

Participants were given three hypothetical case scenarios designed to ascertain GC responses when they encountered a patient who brought their DTC-GT result or TPI data to clinic (Figure 1). Participants were informed that the hypothetical probands in each scenario all had Ashkenazi Jewish (AJ) ancestry, had no previous clinical-grade genetic testing, did not have family members available for testing, had completed their cancer treatment, if applicable, and that the cost of genetic testing was not a factor. Each pedigree was associated with three sub-scenarios: (A) the proband had no prior genetic testing, (B) the proband underwent DTC-GT (23andMe) that reported an AJ pathogenic variant in *BRCA1/2*, and (C) the proband underwent DTC-GT and utilized an online TPI service (Promethease) that reported a non-AJ pathogenic variant in *BRCA1/2*.

Options for genetic testing recommendations were provided as multiple choice questions and included: single-site testing of the reported variant (defined as site-specific testing); the three AJ *BRCA1/2* founder mutations or comprehensive testing of *BRCA1/2* (which were grouped together and defined as gene-specific testing); a breast cancer panel with high and moderate penetrance genes, a breast and gynecological cancer panel with genes related to hereditary breast, ovarian, and gynecological cancer, or a broad cancer panel with genes related to a multitude of different cancer types (which were grouped together and defined as multi-gene testing). The data are summarized in Figure 2.

### *Scenario 1*

The first pedigree (Figure 1a) involved a 37-year-old woman diagnosed with breast cancer at age 33. She has a family history significant for breast cancer diagnosed under age 50 in her mother and maternal cousin and ovarian cancer in her maternal grandmother and maternal aunt. This pedigree is suggestive of HBOC syndrome. All participants (80/80, 100%)

recommended genetic testing for the proband when she presented without prior genetic testing results, with the majority (72/80, 90%) selecting multi-gene testing. If instead this proband presented to clinic with a 23andMe result reporting an AJ founder mutation in *BRCA1/2*, then 77/80 (96%) of participants would recommend confirmatory genetic testing of some degree. When comparing the 77 participants that recommended genetic testing in both conditions, they were more likely to select site-specific or gene-specific testing in the presence of the 23andMe result than when the proband had no previous genetic testing (30/77, 39% v. 7/77, 9%,  $p < 0.01$ ). A free-response text box was provided to participants who did not recommend clinical-grade genetic testing; the three participants each indicated a similar response that they trusted this company to accurately identify the three AJ *BRCA1/2* founder mutations. Alternatively, if this proband presented to clinic with TPI data reporting a non-AJ pathogenic variant in *BRCA1/2*, all participants (80/80, 100%) would recommend clinical-grade testing. Most participants selected a multi-gene testing strategy similar to their recommendations when the proband had no prior genetic testing (64/77, 83% v. 70/77, 90%,  $p = 0.62$ ).

### *Scenario 2*

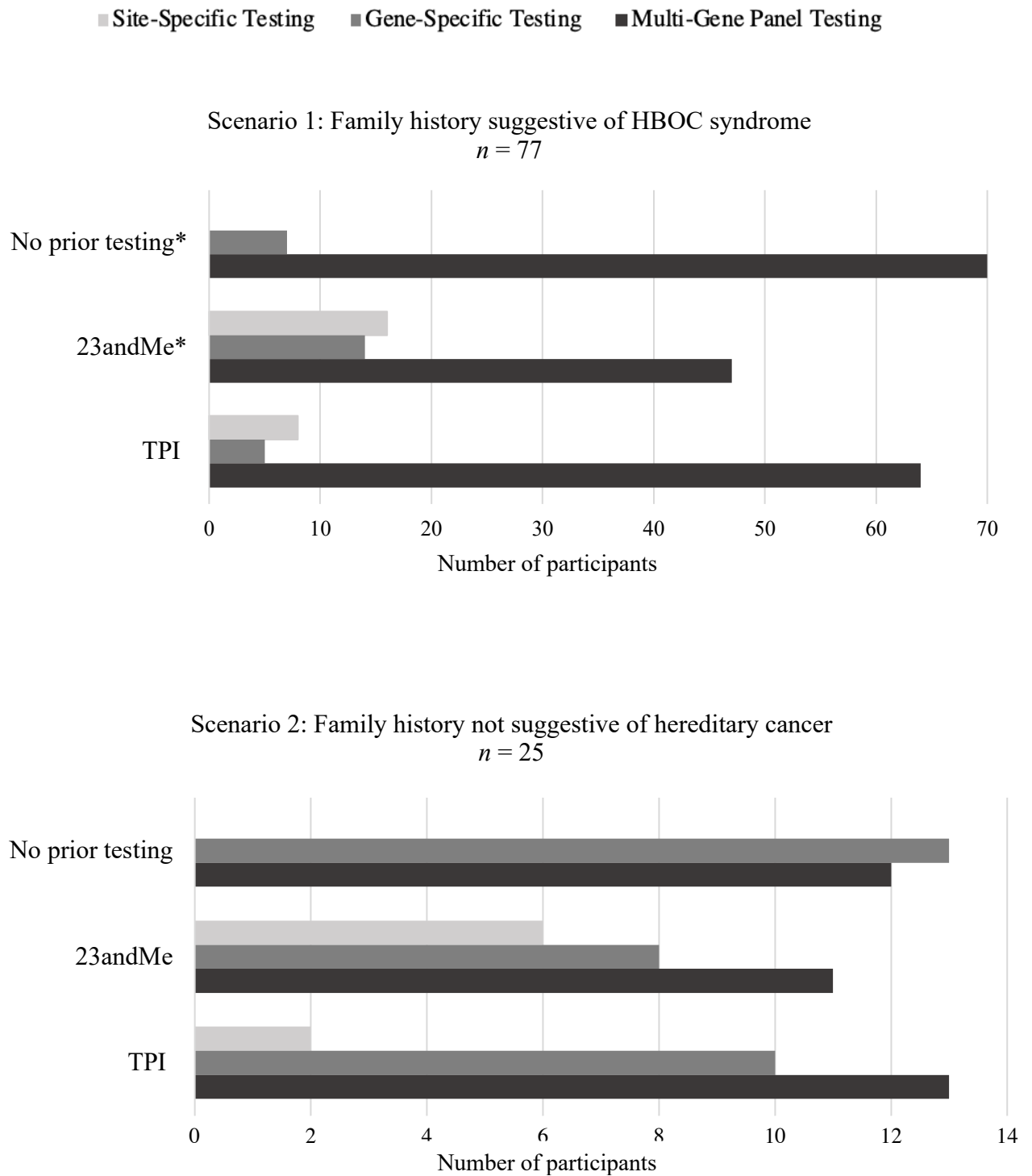
The second pedigree (Figure 1b) involved a 52-year-old woman unaffected with cancer and a family history that is not suggestive of hereditary cancer. Accordingly, a minority of participants (25/80, 32%) recommended genetic testing for the proband when she had no prior genetic testing results. Approximately half of those that did recommend testing (13/25, 52%) selected the three AJ *BRCA1/2* founder mutations. In contrast, if this proband presented to clinic with a 23andMe result reporting an AJ founder mutation in *BRCA1/2*, then the majority of participants (78/80, 97%) would recommend genetic testing. When comparing the 25 participants that recommended testing in both sub-scenarios, about half would still utilize a targeted testing approach of site-specific or gene-specific testing (14/25, 56% v. 13/25, 52%,  $p$

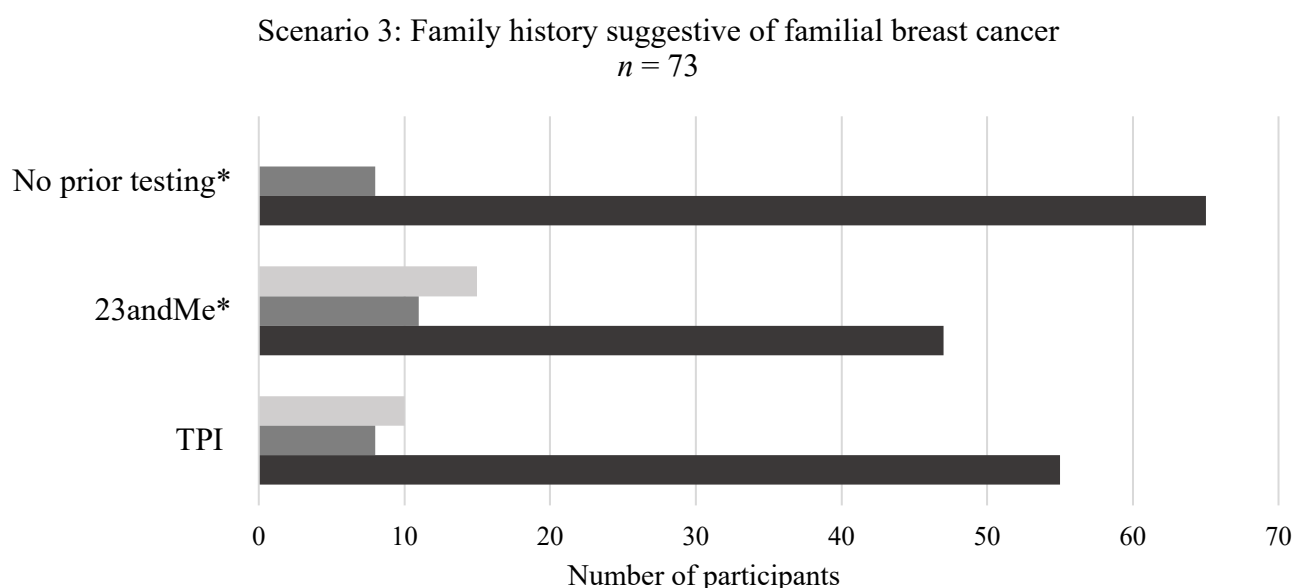
= 0.41). Therefore, the presence of a 23andMe report did not significantly alter the type of testing recommended amongst these GCs. Similarly, when the proband presented with TPI data reporting a non-AJ pathogenic variant in *BRCA1/2*, most GCs (77/80, 96%) would recommend genetic testing, but half of the GCs included in the comparison (12/25, 48%) still selected a targeted testing approach. Awareness of the limitations of DTC-GT and TPI services were cited as the reason amongst participants that did not recommend confirmatory testing.

### *Scenario 3*

The third pedigree (Figure 1c) involved a 60-year-old woman diagnosed with breast cancer at age 56, with a family history of older onset breast cancers possibly suggestive of familial, but not hereditary, breast cancer. As this proband meets NCCN guidelines (version 3.2019) for hereditary breast cancer genetic testing, the majority (73/80, 91%) of participating GCs recommended genetic testing, with most of those (65/73, 89%) recommending multi-gene testing. If this proband presented with a 23andMe result reporting an AJ founder mutation in *BRCA1/2*, then 77/80 (96%) would recommend genetic testing. When comparing the GCs that recommended testing in both scenarios, they were more likely to select site-specific or gene-specific testing in the presence of the 23andMe result than when the proband had no previous genetic testing (26/73, 36% v. 8/73, 11%,  $p < 0.01$ ). Alternatively, if this patient presented with TPI data reporting a non-AJ pathogenic variant in *BRCA1/2*, then 79/80 (99%) of participants would recommend genetic testing and were equally as likely to recommend a multi-gene panel (55/73, 75%, v. 65/73, 89%,  $p > 0.05$ ) as they were when the proband had no prior genetic testing.

**Figure 2.** Genetic testing recommendations grouped by clinical scenario





\*Indicates a significant difference in genetic testing recommendations between conditions ( $p < 0.05$ )

Breakdown of genetic testing types recommended by participants, compared between each clinical scenario. Site-specific testing refers to single-site analysis, gene-specific testing refers to the three Ashkenazi Jewish *BRCA1/2* variants and comprehensive *BRCA1/2* testing, and multi-gene testing includes a breast panel, a breast and gynecological cancer panel, and a broad cancer panel with genes related to a multitude of different cancer types.

TPI = Third-party interpretation

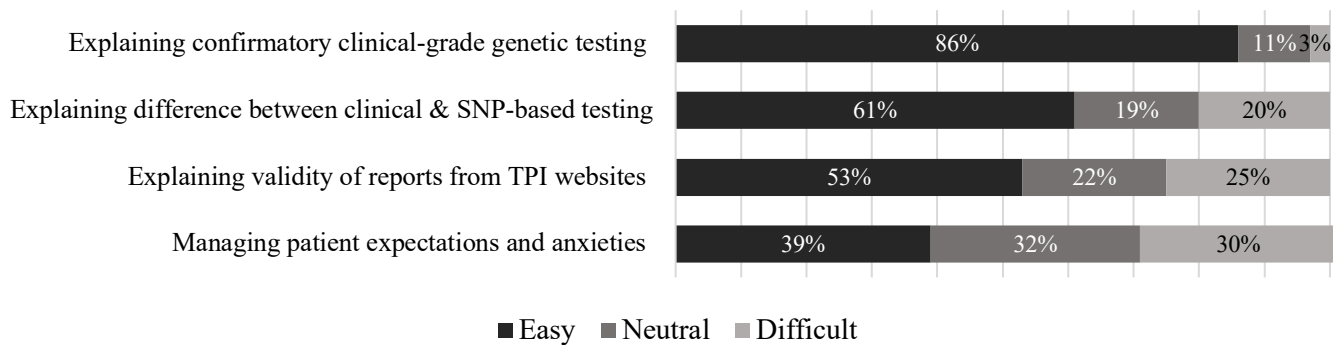
## Challenges Associated with Direct-to-Consumer Genetic Testing Reports and Desired Resources

The majority of participants reported that it is not challenging for them to explain the need for confirmatory clinical-grade genetic testing (69/80, 86%) or the differences between clinical and SNP-based genetic testing (49/80, 61%). Approximately half of participants indicated that it is easy to explain the limited validity of reports from TPI websites (42/80, 53%). Furthermore, 40% (32/80) of participants indicated that managing patient expectations and anxieties is easy, whereas 30% (24/80) indicated that this task is difficult. There was no difference in the perceived level of difficulty of all proposed challenges between recent graduates and more experienced GCs ( $p > 0.05$ ). Nearly 75% (59/80) of participants agreed that a patient education document would be a helpful resource to aid their clinical counseling

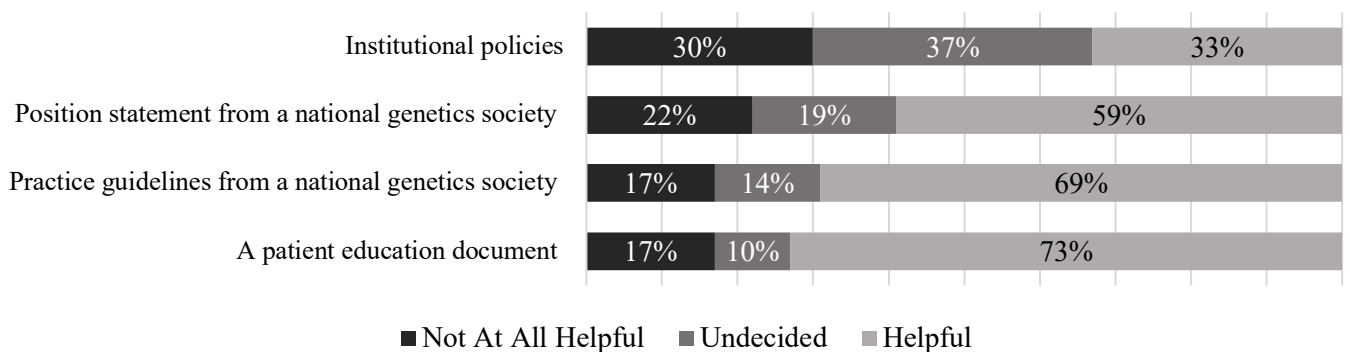
of these patients. They also indicated that practice guidelines (55/80, 69%) or a position statement (47/80, 59%) from a national genetics society would be helpful resources to guide their testing recommendations. These results are further summarized in Figure 3.

**Figure 3.** Likert scale values

#### Challenges associated with counseling on DTC-GT results in clinic



#### Desired resources to aid counseling approaches to patients with DTC-GT



Reported Likert scale values assessing genetic counselors' perceived level of difficulty counseling about DTC-GT results in clinic and desired resources to aid their counseling of these patients.

DTC-GT = Direct-to-consumer genetic testing

SNP = Single nucleotide polymorphism

TPI = Third-party interpretation

## DISCUSSION

Despite the increasing availability of health-related DTC-GT and TPI services, there has been limited research into the intersection between these types of results and GCs approaches to clinical genetic testing recommendations. The results of our study indicate that GCs recommendations are dependent on the personal and family history of the consumer, as well as if the report is from a DTC-GT company or an online TPI service.

### **Recommendations for Direct-to-Consumer Genetic Testing Results**

The majority of participants would recommend confirmatory clinical-grade genetic testing for all probands with DTC-GT results, regardless of their personal or family history. NCCN also recommends confirmatory testing of DTC-GT results because, unlike clinical genetic tests, DTC-GT is not diagnostic, offer risk information for only a limited set of conditions, and may be associated with a higher error rate. For these reasons, DTC-GT results are not intended to impact an individual's medical management and could lead to inappropriate changes in patient care (Tandy-Connor et al., 2018).

When presented with a proband affected with breast cancer (scenarios 1 and 3), the majority of participating GCs recommended multi-gene panel testing. However, if this proband had a 23andMe result for an AJ *BRCA1/2* founder mutation, GCs were overall more likely to target their testing strategy to recommend site-specific or gene-specific testing. This finding suggests that these GCs attributed the proband's cancer history to the variant reported by the DTC-GT company. However, about half of GCs would still continue to recommend a multi-gene panel in the presence of this 23andMe result. In an analysis of 1,000 AJ women with breast cancer, 3% were identified to carry a pathogenic variant in a breast cancer predisposition gene other than *BRCA1/2* (Walsh et al., 2017). This finding demonstrates that more comprehensive panel testing is an appropriate strategy in these women as it can identify

a causative mutation that would otherwise be missed. This may explain why some of our participants still recommended panel testing in the presence of a reported variant that could have explained the presenting cancer history.

In contrast, scenario 2 presented a proband that did not have a diagnosis of cancer or a family history consistent with hereditary cancer. Respondents were equally as likely to recommend a multi-gene panel when she had no prior genetic testing compared to when she had a 23andMe result for an AJ *BRCA1/2* founder mutation. Our findings suggest that the presence of a positive DTC-GT *BRCA1/2* report influenced this set of GCs testing recommendations in the presence of a positive personal and/or family history of cancer (scenarios 1 and 3), but not in the absence of this clinical history (scenario 2).

### **Recommendations for Third-Party Interpretation Data**

Across all clinical scenarios, the presence of TPI data reporting a non-AJ pathogenic variant in *BRCA1/2* did not influence GCs testing recommendations compared to their recommendations when the proband had no previous genetic testing. Under both conditions, the majority of GCs recommended multi-gene panels. They also consistently recommended confirmatory clinical-grade genetic testing for probands with TPI data. While our study was not designed to identify specific factors that influenced the recommendations made by GCs, some of the free responses from participants indicated distrust with the analytic validity of online TPI services to accurately identify pathogenic variants.

These results suggest two key findings related to TPI data and GC recommendations. First, GCs were more likely to attribute the *BRCA1/2* variant reported by the DTC-GT company as contributing to the cancer history than they were variants reported by TPI services. Second, participants may believe DTC-GT companies are more accurate in identifying germline mutations than TPI services. These findings may, in part, be due to the



fact that 23andMe has FDA approval to specifically test for the three AJ *BRCA1/2* founder mutations in their CLIA-certified and CAP-accredited laboratory, whereas there are greater limitations to TPI services, including a 40% false positive rate (Tandy-Connor et al., 2018).

### **Genetic Counselors' Clinical Intersection with Direct-to-Consumer Genetic Testing**

In 2008, 14% of NSGC members practicing across all specialties reported that they had provided counseling related to patients' DTC-GT results (Hock et al., 2011). Our results show a substantial increase in that figure. Amongst our study population of cancer GCs, 94% reported providing counseling for 23andMe DTC-GT results, and nearly 70% have provided counseling for TPI data. The present findings confirm that GCs are increasingly encountering health-related DTC-GT results as this market continues to expand. This may explain why, contrary to the findings of Brett et al. (2012) wherein only 7% of surveyed GCs expressed confidence in accurately interpreting and explaining DTC-GT results, most of our participants reported that it would be easy for them to navigate potentially challenging aspects of counseling about DTC-GT results. Examples include explaining the need for confirmatory clinical-grade genetic testing, the differences between clinical and SNP-based genetic testing, and the validity of reports from TPI services. These are important counseling skills to have as data from previous studies indicate that most consumers do not question the validity of their health-related DTC-GT results and are not seeking further genetic testing (Brett et al., 2012).

Participating GCs were also asked about desired resources to aid their clinical counseling of these patients. The majority indicated that a position statement and/or practice guideline from a national genetics society would be helpful. As previously mentioned, NCCN (2020) advises molecular confirmation of variants identified by commercial companies. In their position statement, NSGC (2019) recommends that "any genetic variants identified in raw data files should be confirmed in a clinical laboratory before being used in healthcare

decision-making.” Most strongly desired among participants was a patient education document summarizing the risks and benefits of DTC-GT, how raw data are analyzed, the types of results that can be obtained, and why confirmatory testing is necessary. Overall, it appears that GCs would utilize and benefit from the creation of additional patient and professional resources.

### **Strengths, Limitations, and Future Directions**

This study described the specific genetic testing recommendations that GCs would make when evaluating a hypothetical patient with positive DTC-GT results or TPI data for hereditary breast cancer. The ability to interrogate GCs’ recommendations for probands both affected and unaffected with cancer allowed us to differentiate that clinical history impacts testing recommendations in the presence of DTC-GT results, but not TPI data. The demographics of our cohort of GCs are consistent with the larger NSGC membership, allowing for generalizability of results.

This study had several limitations. Importantly, GCs with stronger opinions about DTC-GT, or those with greater experience counseling patients for this indication, may have been more likely to respond to the survey in comparison to GCs with neutral opinions or less experience counseling on this topic. This may have led to selection bias within our sample. Therefore, the reported rate that approximately 70-94% of cancer GCs have encountered DTC-GT reports in clinic could be an overestimate.

The survey employed for this study was not a formally validated tool, but rather created by the authors and participants may have interpreted questions differently than intended. The authors recognize that the GC’s risk assessment and genetic testing decision-making process is complex and difficult to capture in a quantitative survey; therefore, certain testing algorithms were simplified. For example, it is an appropriate genetic testing strategy to

initiate testing with the three AJ *BRCA1/2* founder mutations and subsequently reflex to a broader panel if necessary. This survey did not take into account how the option of reflex genetic testing may have influenced participant responses. Lastly, NCCN guidelines were updated after this study concluded to support testing for hereditary breast cancer genes in all individuals with AJ ancestry (as were all hypothetical probands in this study), regardless of their personal cancer status.

While our study captured the genetic testing strategies of GCs specializing in cancer, DTC-GT results have implications for a wide range of disease types and medical specialties. 23andMe issues carrier status reports for more than 40 autosomal recessive conditions and health predisposition reports for various multifactorial conditions. Future research should examine this topic amongst GCs practicing in other specialties to better define how GCs as a whole implement DTC-GT results into clinical practice. Additionally, it may also be interesting to examine the relationship between GCs attitudes towards commercial testing and their recommendations for clinical-grade genetic testing.

### **Practice Implications**

To the best of our knowledge, our study is the first to examine GCs' genetic testing recommendations for patients with DTC-GT results or TPI data. GCs' increasing interaction with patients seeking guidance on these results, as demonstrated by our findings, highlights the importance of understanding their approaches to genetic testing. The majority of participating GCs would recommend confirmatory testing, consistent with guidelines by both NCCN and NSGC. However, existing guidelines do not advise GCs on which type of confirmatory testing to order, which is also reflected in our results. Although participants were more likely to recommend targeted testing in the presence of a positive DTC-GT *BRCA1/2* report for a proband affected with breast cancer, a considerable portion of our sample still recommended a

multi-gene panel. There was also variability in the breadth of recommended testing to confirm variants identified by TPI services. While GCs who participated in our study are unified in their practice of ordering confirmatory testing, the selected clinical-grade test varies depending on the proband's cancer history and whether the report was through DTC-GT or TPI services.

Prior studies have shown that GCs may not believe they have the professional obligation to be knowledgeable about DTC-GT or feel comfortable interpreting these results (Brett et al., 2012; Hock et al., 2011). Given that the majority of participants in our study believed that it would be easy to provide counseling related to DTC-GT, it appears that GCs have made great strides in educating themselves on this topic. As the market for DTC-GT expands and this patient population continues to grow, GCs must continue to be knowledgeable on this topic and remain at the forefront of practice-related conversations.

## APPENDIX

### *Survey Distributed to Genetic Counselors*

#### Qualifying Questions

1. Where do you currently practice as a genetic counselor?
  - ☐ United States
  - ☐ Canada
  - ☐ Other (*disqualifying answer*)
2. Do you consider clinical cancer genetic counseling as your primary specialty (more than 50% of your time)?
  - ☐ Yes
  - ☐ No (*disqualifying answer*)

#### Demographic Questions

1. What is your gender?
  - ☐ Male
  - ☐ Female
  - ☐ Other
  - ☐ Prefer not to answer
2. What is your age? (*text box; require answer to be an integer*)
3. What is your race? (Select all that apply)
  - ☐ American Indian or Alaskan Native
  - ☐ Asian
  - ☐ Asian Indian
  - ☐ Black or African American
  - ☐ Native Hawaiian or other Pacific Islander
  - ☐ White or Caucasian
  - ☐ Prefer not to answer
2. What is your ethnicity?
  - ☐ Hispanic
  - ☐ Non-Hispanic
  - ☐ Prefer not to answer
4. In what region do you practice?
  - ☐ Region 1: CT, MA, ME, NH, RI, VT, CN, Maritime Provinces
  - ☐ Region 2: DC, DE, MD, NJ, NY, PA, VA, WV, PR, VI, Quebec
  - ☐ Region 3: AL, FL, GA, KY, LA, MS, NC, SC, TN
  - ☐ Region 4: AR, IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, OK, SD, WI, Ontario
  - ☐ Region 5: AZ, CO, MT, NM, TX, UT, WY, Alberta, Manitoba, Sask.
  - ☐ Region 6: AK, CA, HI, ID, NV, OR, WA, British Columbia, Yukon

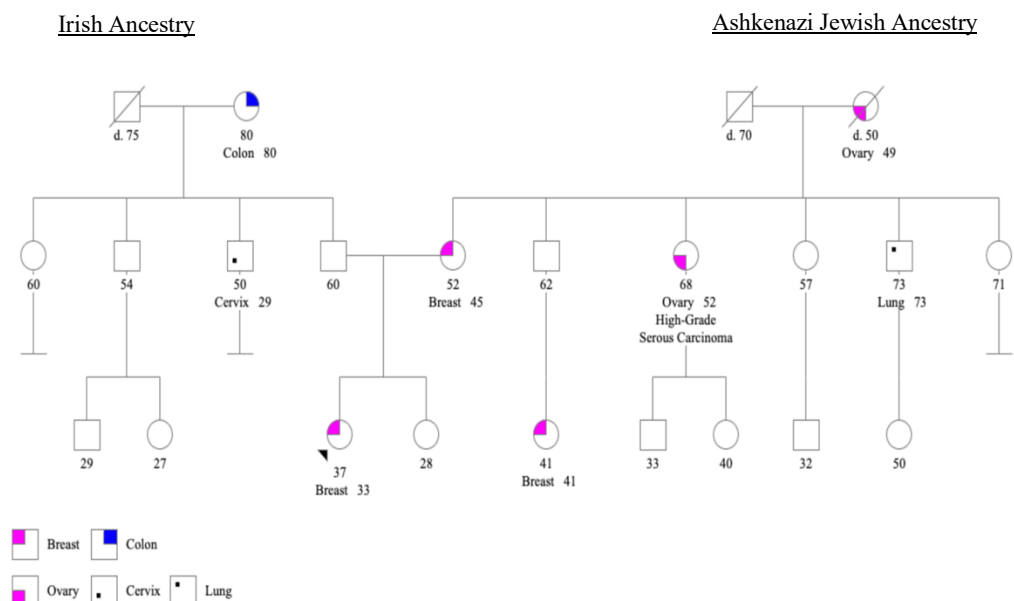
5. Please select which best describes your primary place of employment (Select one):
- ☐ University medical center
  - ☐ University/nonmedical center
  - ☐ Private hospital/medical facility
  - ☐ Public hospital/medical facility
  - ☐ Physician's private practice
  - ☐ Diagnostic laboratory
  - ☐ Health maintenance organization
  - ☐ Telegenetics company
  - ☐ Other (please specify) (*blank text box*)
6. Please enter your graduation year from a genetic counseling training program. (*text box; require answer to be an integer*)
7. How many years in total have you practiced as a clinical cancer genetic counselor? (*text box; require answer to be an integer*)

### **Genetic Counseling Related Questions**

8. Of the patients you have seen in the last year for cancer genetic counseling, approximately what percentage were breast-related indications (personal and/or family histories of breast cancer)?
- ☐ 0%
  - ☐ 25%
  - ☐ 50%
  - ☐ 75%
  - ☐ 100%
9. In general, which of the following factors influence your decision on what genetic testing to recommend for a patient? Please select all that apply:
- ☐ Clinical risk assessment
  - ☐ National Cancer Comprehensive Network (NCCN) guidelines
  - ☐ Insurance coverage
  - ☐ Physician preference
  - ☐ Patient preference
  - ☐ Institutional policies
10. Does your place of employment have a forum to review genetics cases to elicit feedback from genetic counselors and/or other medical providers (i.e. case conference)?
- ☐ Yes
  - ☐ No
11. Which of the following best represents the discussions within your department/institution regarding how to address direct-to-consumer genetic testing results in your clinics?
- ☐ Our department/institution has not had discussions regarding this topic

- Our department/institution has had discussions, but a consensus was not reached on how to address direct-to-consumer genetic testing results in our clinics
  - Our department/institution has developed formal policies (i.e. standard of practice) regarding how to address direct-to-consumer genetic testing results in our clinics
  - Other: please specify
12. Have you ever counseled a patient who referenced (either by having an electronic or physical copy and/or mentioning it in the session) their health-related DTC-GT results in the appointment (for example, 23andMe)? (Not including third party interpretation reports)
- Yes
  - No (*skip to question 14*)
13. In the last year, how many patients have you counseled regarding their health-related DTC-GT results (for example, 23andMe)? (*text box, require answer be an integer*)
14. Have you ever counseled a patient who referenced (either by having an electronic or physical copy and/or mentioning it in the session) a third-party interpretation of their health-related DTC-GT results in the appointment (for example, Promethease or similar websites)?
- Yes
  - No (*skip to next section*)
15. In the last year, how many patients have you counseled regarding a third-party interpretation of their health-related DTC-GT results (for example, Promethease or similar websites)? (*text box, require answer be an integer*)

### Scenario #1



You are counseling this proband. She has no previous clinical genetic testing and has already completed breast cancer treatment before her appointment with you. She reports no one in her family has ever undergone genetic testing and other family members are unavailable for testing. The proband does not currently have insurance but is willing to self-pay for any recommended genetic testing. Consider the following questions and answer according to how you would approach this in your clinical practice:

1. Would you recommend genetic testing for this proband?
  - ☐ Yes
  - ☐ No

*Yes = Give following question.*

*No = Free response question = Please explain your reasoning for not considering genetic testing for this proband.*

2. Which of the following best fits your first-tier approach to genetic testing for this proband?
  - ☐ I would recommend a broad cancer panel associated with a wide range of cancer/tumor types
  - ☐ I would recommend a breast and gynecological cancer focused panel including genes associated with hereditary breast, ovarian, and uterine cancer
  - ☐ I would recommend a breast cancer focused panel including high and moderate penetrant breast cancer related genes
  - ☐ I would recommend the Hereditary Breast and Ovarian Cancer syndrome related genes (*BRCA1* and *BRCA2*)
  - ☐ I would recommend the three Ashkenazi Jewish founder mutations (*BRCA1* 185delAG, *BRCA1* 5382insC, and *BRCA2* 6174delT)

Consider a different scenario for this same proband. The proband reports that she has had DTC-GT, specifically through 23andMe, that she obtained by sending in a saliva sample without direct oversight from a healthcare professional. The DTC-GT company only analyzed the three Ashkenazi Jewish founder mutations associated with Hereditary Breast and Ovarian Cancer syndrome (*BRCA1* 185delAG, *BRCA1* 5382insC, and *BRCA2* 6174delT). They also analyzed other health related-genes outside the context of cancer genetics. The DTC-GT results identified the following variant in the proband: *BRCA1* 185delAG. Consider the following questions:

1. Would you recommend additional genetic testing for this proband?
  - ☐ Yes
  - ☐ No

*Yes = Give following question.*

*No = Free response question = Please explain your reasoning for not considering genetic testing for this proband.*

2. Which of the following best fits your first-tier approach to genetic testing for this proband?



- I would recommend a broad cancer panel associated with a wide range of cancer/tumor types, which would include the *BRCA1* 185delAG variant
- I would recommend a breast and gynecological cancer focused panel, which would include the *BRCA1* 185delAG variant
- I would recommend a breast cancer focused panel including high and moderate penetrant breast cancer related genes of which would include the *BRCA1* 185delAG variant
- I would recommend the Hereditary Breast and Ovarian Cancer syndrome related genes (*BRCA1* and *BRCA2*), which would include the *BRCA1* 185delAG variant.
- I would recommend the three Ashkenazi Jewish founder mutations (*BRCA1* 185delAG, *BRCA1* 5382insC, and *BRCA2* 6174delT)
- I would recommend single-site testing of the specific *BRCA1* 185delAG variant identified by the DTC-GT report

Consider a different scenario for this same proband. The proband reports she has had DTC-GT. The DTC-GT company only analyzed the three Ashkenazi Jewish founder mutations associated with Hereditary Breast and Ovarian Cancer syndrome (*BRCA1* 185delAG, *BRCA1* 5382insC, and *BRCA2* 6174delT). They also analyzed other health related-genes outside the context of cancer genetics. No relevant variants were detected in cancer related genes. The proband then elected to download her raw data from the DTC-GT company's website and upload it to a third-party interpretation website, specifically Promethease. The proband presents for genetic counseling with results from the third-party interpretation website that reported the following: "*BRCA1* variant c.3748G>T considered pathogenic for breast cancer." Consider the following questions:

1. Would you recommend additional genetic testing for this proband?
  - Yes
  - No

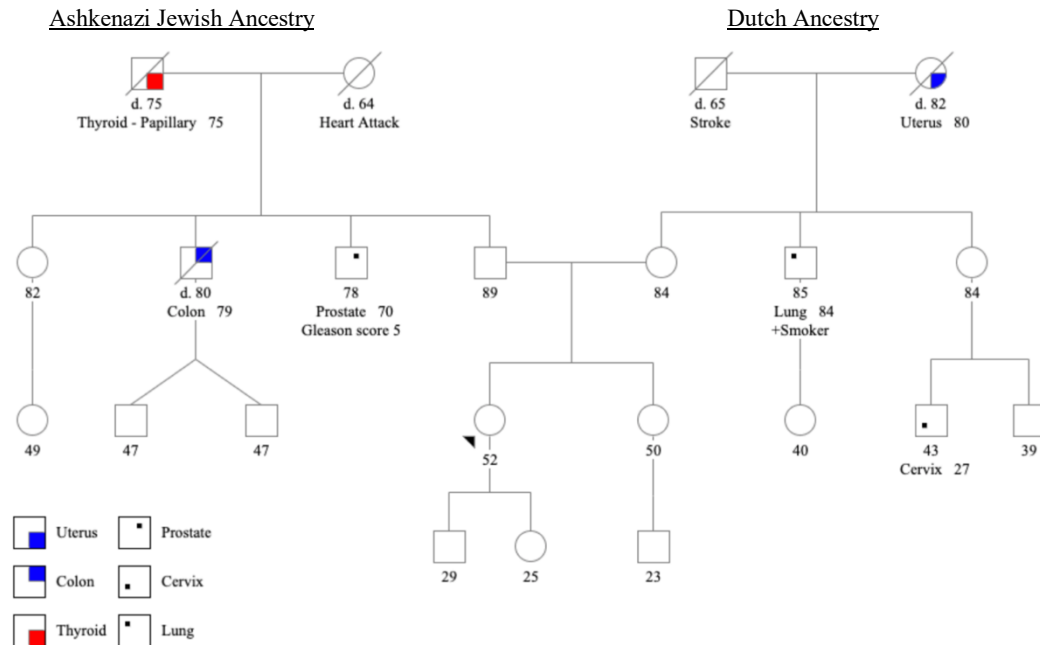
*Yes = Give following question.*

*No = Free response question = Please explain your reasoning for not considering genetic testing for this proband.*

2. Which of the following best fits your first-tier approach to genetic testing for this proband?
  - a. I would recommend a broad cancer panel associated with a wide range of cancer/tumor types, which would include the *BRCA1* c.3748G>T variant
  - b. I would recommend a breast and gynecological cancer focused panel, which would include the *BRCA1* c.3748G>T variant
  - c. I would recommend a breast cancer focused panel including high and moderate penetrant breast cancer related genes, which would include the *BRCA1* c.3748G>T variant
  - d. I would recommend the Hereditary Breast and Ovarian Cancer syndrome related genes (*BRCA1* and *BRCA2*), which would include the *BRCA1* c.3748G>T variant
  - e. I would recommend the three Ashkenazi Jewish founder mutations (*BRCA1* 185delAG, *BRCA1* 5382insC, and *BRCA2* 6174delT)

- f. I would recommend single-site testing of the specific *BRCA1* c.3748G>T variant identified by the third-party interpretation website

### Scenario #2



You are counseling this proband. She has no previous clinical genetic testing and reports a history of normal breast screenings and no history of breast biopsies. She reports no one in her family has ever undergone genetic testing and other family members are unavailable for testing. The proband does not currently have insurance but is willing to self-pay for any recommended genetic testing. Consider the following questions and answer according to how you would approach this in your clinical practice.

1. Would you recommend genetic testing for this proband?

- ☐ Yes
- ☐ No

*Yes = Give following question.*

*No = Free response question = Please explain your reasoning for not considering genetic testing for this proband.*

2. Which of the following best fits your first-tier approach to genetic testing for this proband?

- ☐ I would recommend a broad cancer panel associated with a wide range of cancer/tumor types
- ☐ I would recommend a breast and gynecological cancer focused panel including genes associated with hereditary breast, ovarian, and uterine cancer

- I would recommend a breast cancer focused panel including high and moderate penetrant breast cancer related genes
- I would recommend the Hereditary Breast and Ovarian Cancer syndrome related genes (*BRCA1* and *BRCA2*)
- I would recommend the three Ashkenazi Jewish founder mutations (*BRCA1* 185delAG, *BRCA1* 5382insC, and *BRCA2* 6174delT)

Consider a different scenario for this same proband. The proband reports that she has had DTC-GT, specifically through 23andMe, that she obtained by sending in a saliva sample without direct oversight from a healthcare professional. The DTC-GT company only analyzed the three Ashkenazi Jewish founder mutations associated with Hereditary Breast and Ovarian Cancer syndrome (*BRCA1* 185delAG, *BRCA1* 5382insC, and *BRCA2* 6174delT). They also analyzed other health related-genes outside the context of cancer genetics. The DTC-GT results identified the following variant in the proband: *BRCA2* 6174delT. Consider the following questions:

1. Would you recommend additional genetic testing for this proband?
  - Yes
  - No

*Yes = Give following question.*

*No = Free response question = Please explain your reasoning for not considering genetic testing for this proband.*

2. Which of the following best fits your first tier approach to genetic testing for this proband?
  - I would recommend a broad cancer panel associated with a wide range of cancer/tumor types, which would include the *BRCA2* 6174delT variant
  - I would recommend a breast and gynecological cancer focused panel, which would include the *BRCA2* 6174delT variant
  - I would recommend a breast cancer focused panel including high and moderate penetrant breast cancer related genes, which would include the *BRCA2* 6174delT variant
  - I would recommend Hereditary Breast and Ovarian Cancer syndrome related genes (*BRCA1* and *BRCA2*), which would include the *BRCA2* 6174delT variant
  - I would recommend the three Ashkenazi Jewish founder mutations (*BRCA1* 185delAG, *BRCA1* 5382insC, and *BRCA2* 6174delT)
  - I would recommend single-site testing of the specific *BRCA2* 6174delT variant identified by the DTC-GT report

Consider a different scenario for this same proband. The proband reports she has had DTC-GT. The DTC-GT company only analyzed the three Ashkenazi Jewish founder mutations associated with Hereditary Breast and Ovarian Cancer syndrome (*BRCA1* 185delAG, *BRCA1* 5382insC, and *BRCA2* 6174delT). They also analyzed other health related-genes outside the context of cancer genetics. No relevant variants were detected in cancer related genes. The proband then elected to download her raw data from the DTC-GT company's website and upload it to a third-party interpretation website, specifically Promethease. The proband presents for genetic counseling with results from the third-party interpretation website that

reported the following: “*BRCA2* variant aka c.7007G>A considered pathogenic for breast cancer.” Consider the following questions:

1. Would you recommend additional genetic testing for this proband?
  - ☐ Yes
  - ☐ No

*Yes = Give following question.*

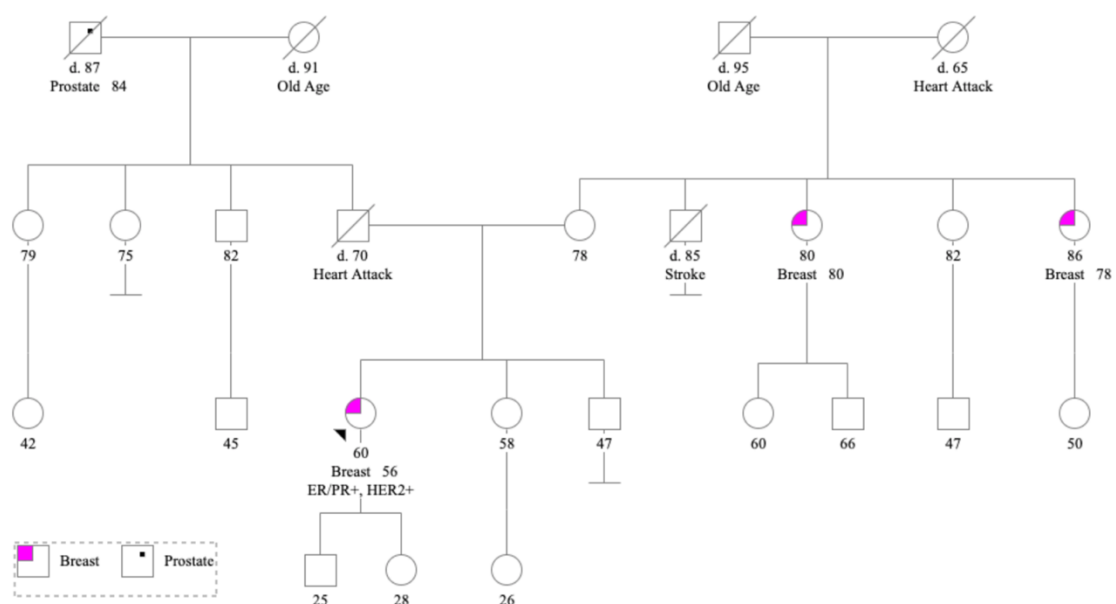
*No = Free response question = Please explain your reasoning for not considering genetic testing for this proband.*

2. Which of the following best fits the first-tier approach to genetic testing for this proband?
  - ☐ I would recommend a broad cancer panel associated with a wide range of cancer/tumor types, which would include the *BRCA2* c.7007G>A variant
  - ☐ I would recommend a breast and gynecological cancer focused panel, which would include the *BRCA2* c.7007G>A variant
  - ☐ I would recommend a breast cancer focused panel including high and moderate penetrant breast cancer related genes, which would include the *BRCA2* c.7007G>A variant
  - ☐ I would recommend Hereditary Breast and Ovarian Cancer syndrome related genes (*BRCA1* and *BRCA2*), which would include the *BRCA2* c.7007G>A variant
  - ☐ I would recommend the three Ashkenazi Jewish founder mutations (*BRCA1* 185delAG, *BRCA1* 5382insC, and *BRCA2* 6174delT)
  - ☐ Single-Site testing of the specific *BRCA2* 7007G>A variant identified by the third-party interpretation website.

### Scenario #3

#### English Ancestry

#### Ashkenazi Jewish Ancestry



You are counseling this proband. She has no previous clinical genetic testing and has already completed breast cancer treatment before her appointment with you. She reports no one in her family has ever undergone genetic testing and other family members are unavailable for testing. The proband does not currently have insurance but is willing to self-pay for any recommended genetic testing. Consider the following questions and answer according to how you would approach this in your clinical practice.

1. Would you recommend genetic testing for this proband?
  - ☐ Yes
  - ☐ No

*Yes = Give following question.*

*No = Free response question = Please explain your reasoning for not considering genetic testing for this proband.*

2. Which of the following best fits your first-tier approach to genetic testing for this proband?
  - ☐ I would recommend a broad cancer panel associated with a wide range of cancer/tumor types
  - ☐ I would recommend a breast and gynecological cancer focused panel including genes associated with hereditary breast, ovarian, and uterine cancer
  - ☐ I would recommend a breast cancer focused panel including high and moderate penetrant breast cancer related genes
  - ☐ I would recommend Hereditary Breast and Ovarian Cancer syndrome related genes (*BRCA1* and *BRCA2*) only
  - ☐ I would recommend the three Ashkenazi Jewish founder mutations (*BRCA1* 185delAG, *BRCA1* 5382insC, and *BRCA2* 6174delT) only

Consider a different scenario for this same proband. The proband reports that she has had DTC-GT, specifically through 23andMe, that she obtained by sending in a saliva sample without direct oversight from a healthcare professional. The DTC-GT company only analyzed the three Ashkenazi Jewish founder mutations associated with Hereditary Breast and Ovarian Cancer syndrome (*BRCA1* 185delAG, *BRCA1* 5382insC, and *BRCA2* 6174delT). They also analyzed other health related-genes outside the context of cancer genetics. The DTC-GT results identified the following variant in the proband: *BRCA1* 5382insC. Consider the following questions:

1. Would you recommend additional genetic testing for this proband?
  - ☐ Yes
  - ☐ No

*Yes = Give following question.*

*No = Free response question = Please explain your reasoning for not considering genetic testing for this proband.*

2. Which of the following best fits your first tier approach to genetic testing for this proband?

- I would recommend a broad cancer panel associated with a wide range of cancer/tumor types, which would include the *BRCA1* 5382insC variant
- I would recommend a breast and gynecological cancer focused panel, which would include the *BRCA1* 5382insC variant
- I would recommend a breast cancer focused panel including high and moderate penetrant breast cancer related genes, which would include the *BRCA1* 5382insC variant
- I would recommend Hereditary Breast and Ovarian Cancer syndrome related genes (*BRCA1* and *BRCA2*), which would include the *BRCA1* 5382insC variant
- I would recommend the three Ashkenazi Jewish founder mutations (*BRCA1* 185delAG, *BRCA1* 5382insC, and *BRCA2* 6174delT)
- I would recommend single-site testing of the specific *BRCA1* 5382insC variant identified by the DTC-GT report

Consider a different scenario for this same proband. The proband reports she has had DTC-GT. The DTC-GT company only analyzed the three Ashkenazi Jewish founder mutations associated with Hereditary Breast and Ovarian Cancer syndrome (*BRCA1* 185delAG, *BRCA1* 5382insC, and *BRCA2* 6174delT). They also analyzed other health related-genes outside the context of cancer genetics. No relevant variants were detected in cancer related genes. The proband then elected to download her raw data from the DTC-GT company's website and upload it to a third-party interpretation website, specifically Promethease. The proband presents for genetic counseling with results from the third-party interpretation website that reported the following: "*BRCA1* variant aka c.5095C>T considered pathogenic for breast cancer." Consider the following questions:

1. Would you recommend additional genetic testing for this proband?
  - Yes
  - No

*Yes = Give following question.*

*No = Free response question = Please explain your reasoning for not considering genetic testing for this proband.*

2. Which of the following best fits the first-tier approach to genetic testing for this proband?
  - I would recommend a broad cancer panel associated with a wide range of cancer/tumor types, which would include the *BRCA1* c.5095C>T variant
  - I would recommend a breast and gynecological cancer focused panel, which would include the *BRCA1* c.5095C>T variant
  - I would recommend a breast cancer focused panel including high and moderate penetrant breast cancer related genes, which would include the *BRCA1* c.5095C>T variant
  - I would recommend the Hereditary Breast and Ovarian Cancer syndrome related genes (*BRCA1* and *BRCA2*), which would include the *BRCA1* c.5095C>T variant
  - I would recommend the three Ashkenazi Jewish founder mutations (*BRCA1* 185delAG, *BRCA1* 5382insC, and *BRCA2* 6174delT)

- I would recommend single-site testing of the specific *BRCA1* c.5095C>T variant identified by the third-party interpretation website

#### Educational/Resource Questions

1. In your genetic counseling graduate school training, did you receive information regarding DTC-GT?
  - Yes
  - No
2. Please indicate how you received information regarding DTC-GT in your training program: (select all that apply)
  - Class lectures
  - Clinical rotations
  - Journal club
  - Case conferences
  - Research articles
  - Other (Please specify): *(text box)*
3. Have you attended any online seminars or talks at educational conferences regarding DTC-GT?
  - Yes
  - No

Please indicate how easy or difficult you may find the following scenarios associated with counseling about DTC-GT in clinic:

	Very Easy	Easy	Neutral	Difficult	Very Difficult
Explaining the difference between clinical genetic testing versus SNP-based genetic testing	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Explaining the validity of the reports from third-party interpretation websites	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Explaining the need for clinical confirmatory genetic testing	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Explaining that DTC-GT is not comprehensive genetic testing	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Managing patient expectations and anxieties	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

- 4.
5. What is the most notable challenge(s) that you face when counseling about DTC-GT in clinic? *(text box, free response)*

Please indicate which of the following resources would be helpful regarding counseling about DTC-GT results:

	Not at all helpful	Slightly helpful	Undecided	Very Helpful	Extremely helpful
Practice guidelines from a local and/or national genetics society	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Position statement from a local and/or national genetics society	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Institutional policies	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
A patient education document	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

6.

7. In addition to the resources listed above, are there any other resources that would be helpful regarding counseling about DTC-GT results? *(text box, free response)*



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## VITA

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