Assessing Genetic Counselors' Clinical Approach and Practices Regarding Pathogenic/Likely Pathogenic Variant Downgrades

Grant Bonesteel

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ASSESSING GENETIC COUNSELORS’ CLINICAL APPROACH AND PRACTICES REGARDING PATHOGENIC/LIKELY PATHOGENIC VARIANT DOWNGRADES

by

Grant William Bonesteel, BA

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ASSESSING GENETIC COUNSELORS’ CLINICAL APPROACH AND PRACTICES REGARDING PATHOGENIC/LIKELY PATHOGENIC VARIANT DOWNGRADES

A

THESIS

Presented to the Faculty of

The University of Texas

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of the Requirements

for the Degree of

MASTER OF SCIENCE

by

Grant William Bonesteele, BA

Houston, Texas

May 2021
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I would like to extend a special thank you to Grace Tran, for her tireless effort and contribution throughout the entire research process. I would also like to thank my thesis committee members who have helped guide and focus my research. Finally, I would like to thank the UTGCP program for their support.
ABSTRACT

Although rare, variant downgrades from a pathogenic/likely pathogenic (P/LP) variant to a variant of uncertain significance can have a significant impact on patients and their families in the clinical cancer setting. However, there is a lack of literature about how to approach these potentially challenging cases as a genetic counselor. Therefore, we aimed to characterize genetic counselors’ experiences, approach, and practices to variant downgrade cases using an online survey. The survey asked participants how they would approach variant downgrade scenarios involving the CDH1 or ATM genes with variable family histories. Genetic counselors appear to be united in whether they would discuss how the variant reclassification was reached, the possibility of another reclassification in the future, and implications for family members across the three variant downgrade scenarios. However, there was variability regarding the management of the proband and the recruitment of family members for family studies of the specific variant between variant downgrade scenarios. This difference in participants’ approach could be attributed to factors such as family history or gene penetrance. Still, participants exhibited the practice-based competencies outlined by ACGC and considered other factors in addition to genetic testing results. We also explored potential challenges that genetic counselors face in variant downgrade cases and found that most genetic counselors agree that counseling a patient who underwent a risk-reducing surgery prior to the variant downgrade (91%) or a patient with a variant downgrade in highly penetrant gene (64%) would be difficult. Common themes in genetic counselors’ experiences with variant downgrades included psychosocial concerns and challenges related to surgery or family history. The genetic testing laboratory that performed testing was the most common resource utilized by genetic counselors during variant downgrade cases. Ultimately, this study provides insight
into how counselors approach variant downgrade cases, what challenges can occur, and what resources would be helpful in these cases.
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INTRODUCTION

In the clinical cancer setting, hereditary cancer genetic testing has become an important aspect of patient care. Clinical testing laboratories have adopted the consensus standards and guidelines for variant interpretation published by the American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP), and variant classifications are based on all the available data at the time of testing. As such, genetic testing can identify variants that are classified as benign (B), likely benign (LB), variant of uncertain significance (VUS), likely pathogenic (LP), and pathogenic (P). The identification of a P/LP variant related to an increased cancer risk may lead to changes in screening or prevention recommendations for the patient depending on whether there are established guidelines for management in a particular gene. For example, women identified with a P/LP variant in the BRCA1/2 genes are recommended to undergo breast MRIs/mammograms, risk-reducing mastectomy, and/or risk-reducing bilateral salpingo-oopherectomy based on guidelines published by the National Comprehensive Cancer Network (NCCN). On the other hand, NCCN and other professional organizations do not recommend increased screening or prevention for patients based on B/LB/VUS. As such, variant interpretation and classification are integral to ensure proper management of a patient undergoing genetic testing for a hereditary cancer syndrome.

There are nuances to the interpretation of genetic testing that make counseling these results more challenging. Genetic counselors are trained to consider other factors when interpreting genetic test results, such as a patient’s family history or the penetrance of a particular gene, as they can alter medical management of a patient. For example, as outlined in the recently updated hereditary diffuse gastric cancer (HDGC) guidelines, a patient with a suggestive family history and no P/LP variant identified in the CDH1 or CTTNA1 gene is still recommended to undergo increased endoscopic screening. Furthermore, penetrance can impact cancer risk estimates and medical management recommendations. For example, there is currently insufficient evidence for recommendations of preventative surgeries based solely on the identification of a P/LP variant in moderately penetrant genes given the lower cancer risks associated with these genes compared to highly penetrant genes. Yet some studies have shown
that there is variability regarding patients’ surgical decisions when a VUS result is identified. This variability may be explained by a combination of factors including prediction of cancer risk based on risk models, family history, patient preference, and misunderstanding of VUS results. Collectively, these studies illustrate the spectrum of factors to consider when interpreting and communicating genetic test results and the importance of comprehensive genetic counseling.8,9

In addition to these challenges, interpretation of genetic testing results can be further complicated by variant reclassifications. This is most prominent in cases regarding VUS results since, at the moment of interpretation, there is insufficient evidence to define their impact on cancer risks. However, as more evidence is collected, a VUS can be reclassified. Factors such as the presence or absence of cancer in additional families with the variant and/or further functional studies can help with variant reclassifications.1,10,11 The majority of VUSs are reclassified to a B/LB variant, and this type of reclassification should have minimal clinical impact for a patient and their family because they are all considered non-actionable results. Less frequently, a VUS can be reclassified to a P/LP variant which can lead to increased cancer screenings or surgical recommendations.2,10,11

Even less frequently, variant downgrades, specifically a P/LP variant downgraded to a lower classification, can occur.10,11 Although rare, studies have pointed out that variant downgrades can have a significant impact on patients. Specifically, patients and their families may have followed rigorous increased cancer screenings, underwent prophylactic surgeries, or made reproductive decisions that were, in retrospect, not indicated based on genetic test results.12-14 Little is known about the perspective of patients who had their P/LP variant downgraded, but one study described a patient who underwent risk-reducing bilateral mastectomy after identification of a TP53 LP variant and expressed anger after it was downgraded to a VUS.15 Furthermore, there is a lack of literature regarding genetic counselors’ experiences with and practices in these rare cases. Therefore, this study aims to assess genetic counselors’ experiences with, and clinical approach and practices regarding cases that involve P/LP downgrades in the clinical cancer setting. By characterizing genetic counselors’ experiences and practices, we hope to better understand what challenges to anticipate, identify helpful resources, and
ultimately, better counsel patients and their families in these unique situations. Given the far-reaching implications of variant downgrades on the patients and their families, research in this area can inform genetic counselors’ approaches and improve patient outcomes in the future.

METHODS

Participants

Cancer genetic counselors who were full members of the National Society of Genetic Counselors or American Board of Genetic Counseling (ABGC) were recruited via email and through the NSGC Student Research Survey Program listserv. Participation in the survey constituted consent to the study, and counselors could opt to discontinue at any point in the survey. The inclusion criteria consisted of (1) being a board certified or board eligible genetic counselor in the US or Canada and (2) dedicating time towards clinical cancer genetic counseling. These criteria excluded participants who had different experience and expertise than required for this study. There were approximately 4,000 full members of NSGC at the time of the study.

Procedures and Instrumentation

The survey was created by the authors using Qualtrics (Qualtrics, Provo, UT) available through the University of Texas Health Science Center at Houston. It was distributed via email to members of NSGC in August 2020. Two reminder emails were sent in September and October 2020. Due to low participant recruitment, the survey was also distributed to the members of ABGC in October 2020. The invitation to participate included: (a) purpose of the study; (b) time needed to complete the survey (~20-25 minutes); (c) the option to confidentially provide an email address to be entered into a drawing to win one of two $50 Amazon gift cards; and (d) the survey link. The survey was closed in January 2021.

The survey was a semi-structured questionnaire with 51 questions. There were eight demographic questions that collected information about schooling, workforce, and years of experience. The next section evaluated genetic counselors’ experience with variant downgrade cases. Variant downgrades were specifically defined as variants with a P/LP classification which was downgraded to a
lower classification (VUS, LB, B). This was differentiated from variant reclassifications which were defined as variants that were reclassified to any other classification.

First, participants were asked how they would counsel a proband who was identified with a BRCA1 VUS that was later reclassified to either a LB or P variant (Figure 1a). The next three scenarios were randomized and assessed genetic counselors’ practices regarding variant downgrades involving LP variants in the CDH1 or ATM genes and variable family histories (Figure 1b-d). For the purpose of this study, one CDH1 scenario included a family history suggestive of HDGC defined as CDH1+fhx and the other pedigree lacked a family history of gastric cancer and is defined as CDH1-fhx.

Figure 1a. BRCA1 VUS reclassification scenario: Participants responded to how they would counsel the proband after the identification of a BRCA1 VUS that was later reclassified to a likely benign or pathogenic variant.
Figure 1b. ATM scenario: Participants responded to how they would counsel the proband after the identification of a likely pathogenic variant in the ATM gene. The patient received increased breast cancer screening prior to a variant downgrade from likely pathogenic to a VUS. Then participants provided their counseling approach regarding the ATM variant downgrade.
Figure 1c-d. *CDH1*+/-fhx scenarios: Participants responded to how they would counsel the proband after the identification of a likely pathogenic variant in the *CDH1* gene. The patient received increased breast cancer screening and a prophylactic gastrectomy prior to a variant downgrade from likely pathogenic to VUS. Then participants provided their counseling approach regarding the *CDH1* variant downgrade.
We followed the hypothetical case scenarios with questions that asked participants to rate various variant downgrade scenarios on a scale from very easy to very difficult. Lastly, genetic counselors who reported experience with variant downgrade cases were asked about the challenges they encountered and the resources they used (See appendix for complete copy of survey). All research protocols met the requirements of the University of Texas Health Committee for the Protection of Human Subjects, and this study was assigned approval number HSC-MS-20-0602.

Data Analysis

STATA (v13.1, College Station, TX) software was used to analyze statistics. Secondary comparative analysis of participants’ answers between scenarios was performed using McNemar's test. Specifically, McNemar’s test was used to evaluate if participants’ answers between scenarios were different due to chance or due to differences among scenarios. All comparative tests were considered significant at type I error rate of 5%. Free text responses were analyzed using inductive analysis, where the data is coded independently of the specific questions that were asked of the participants and emerging themes were identified. Free text responses were analyzed independently by primary investigators (G.B. and G.T.) and highlighted. From the highlighted text, potential themes were identified independently. The primary investigators consulted with each other to review the independently defined themes and coding discrepancies were discussed until a consensus was reached.

RESULTS

Demographics

There were 1,159 cancer genetic counselors eligible to participate in this study based on the NSGC professional status survey published in 2020. There were 165 responses to the survey, yielding an estimated response rate of 14%. Of the 165 participants, 54 did not complete the variant downgrade scenarios and were therefore excluded from analysis. Additionally, 24 participants were excluded from the study because they met the exclusion criteria of working outside of the United States of America and Canada or they did not work primarily in the clinical cancer setting. Ultimately, 87 responses were
included in the analysis. The majority of participants self-identified as female (81/87, 93.1%), non-Hispanic (85/87, 97.7%), white or Caucasian (81/87, 93.10%), and they were employed at university medical centers (39/87, 44.8%). This is representative of the respondents who participated in the 2020 NSGC Professional Status Survey, with the exception that a larger majority of our participants were employed at a university medical center. Full demographic information is displayed in Table 1.¹⁷
<table>
<thead>
<tr>
<th>Demographic Category</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>81 (93)</td>
</tr>
<tr>
<td>Male</td>
<td>6 (7)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>White or Caucasian</td>
<td>81 (93)</td>
</tr>
<tr>
<td>Asian Indian</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>Prefer not to answer</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>85 (98)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Prefer not to answer</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Institution Type</strong></td>
<td></td>
</tr>
<tr>
<td>University medical center</td>
<td>39 (45)</td>
</tr>
<tr>
<td>University/nonmedical center</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Public hospital/medical facility</td>
<td>19 (22)</td>
</tr>
<tr>
<td>Private hospital/medical facility</td>
<td>17 (19)</td>
</tr>
<tr>
<td>Diagnostic laboratory</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Telegenetics company</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Health maintenance organization</td>
<td>3 (3)</td>
</tr>
<tr>
<td><strong>Number of years practicing in cancer genetics</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>51 (59)</td>
</tr>
<tr>
<td>5-10 years</td>
<td>30 (34)</td>
</tr>
<tr>
<td>&gt;10 years</td>
<td>6 (7)</td>
</tr>
</tbody>
</table>

Table 1. Demographics of participants (n=87)
Experience with Variant Downgrades

To better understand genetic counselors’ experience with variant downgrades, participants were asked a series of questions regarding the number of patients they have counseled with variant downgrades. Nearly 78% (68/87) of participants have had at least one variant downgrade case in their career. In the year 2020, approximately 43% (37/87) of participants counseled 1-5 variant downgrade cases compared to approximately 6% (5/87) who reported experience with counseling more than 25 variant downgrade cases. When looking at participants’ experience over their entire career, 32% (28/87) of respondents counseled 1-5 variant downgrades, while 20% (18/87) indicated that they had counseled over 25 cases in their career (Figure 2).

Figure 2. Participants’ experience with variant downgrades

**BRCA1 VUS reclassification**

Participants were asked a series of questions based on a hypothetical scenario involving a BRCA1 VUS that was reclassified to a LB or P variant. A majority of participants agreed that risk reducing mastectomy (80/87, 92%), risk reducing salpingo-oopherectomy (81/87, 93%), breast MRI/mammogram (84/87, 98%), consideration of CA-125 and transvaginal ultrasounds (71/87, 82%), or genetic testing for family members (82/87, 94%) were appropriate if the BRCA1 VUS was reclassified to
a pathogenic variant, but thought they were inappropriate if the BRCA1 VUS was reclassified to a likely benign variant (Figure 3). Additionally, participants were more likely to change recommendations for the proband’s family if the BRCA1 VUS was reclassified to a pathogenic variant, rather than a benign variant (p<0.001) (Supplementary Table 1). Participants reported that variant reclassification and the proband’s personal history were the most important factors influencing their counseling. However, a larger portion of participants felt that the proband’s family history impacted their counseling when the BRCA1 VUS was reclassified to a likely benign variant (Supplementary Figure 1).

Figure 3. Agreement of participants on proband management after BRCA1 reclassification

**CDH1 and ATM downgrades**

In scenarios b-d, participants were asked a series of questions to characterize genetic counselors’ counseling approach regarding variant downgrades from a likely pathogenic variant to a VUS. These scenarios involved a highly penetrant gene, CDH1 +f/hx/-f/hx and a moderately penetrant gene, ATM.

First, we assessed participants’ counseling approach to the likely pathogenic variant. Table 2 summarizes the information genetic counselors would discuss with patients in all three scenarios. Genetic counselors were unified in their counseling approach with the exception of discussing prophylactic surgery. While a vast majority of participants would discuss prophylactic surgery in both CDH1 scenarios, only 34% of participants (30/87) would discuss this aspect in the ATM scenario.
<table>
<thead>
<tr>
<th>Counseling approach to a likely pathogenic variant</th>
<th>(CDH1+fhx) n (%)</th>
<th>(CDH1-fhx) n (%)</th>
<th>(ATM) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discuss how the likely pathogenic classification was reached (lines of evidence)</td>
<td>47 (54)</td>
<td>54 (62)</td>
<td>44 (51)</td>
</tr>
<tr>
<td>Discuss the possibility of variant reclassification</td>
<td>49 (56)</td>
<td>62 (71)</td>
<td>48 (55)</td>
</tr>
<tr>
<td>Discuss cancer risk estimates associated with a germline likely pathogenic variant</td>
<td>85 (98)</td>
<td>84 (97)</td>
<td>84 (97)</td>
</tr>
<tr>
<td>Discuss implications for family members</td>
<td>85 (98)</td>
<td>84 (97)</td>
<td>83 (95)</td>
</tr>
<tr>
<td>Provide patient friendly resources</td>
<td>83 (95)</td>
<td>80 (92)</td>
<td>80 (92)</td>
</tr>
<tr>
<td>Discuss cancer screenings</td>
<td>84 (97)</td>
<td>84 (97)</td>
<td>76 (87)</td>
</tr>
<tr>
<td>Discuss prophylactic surgery</td>
<td>82 (95)</td>
<td>81 (94)</td>
<td>30 (34)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (5)</td>
<td>14 (16)</td>
<td>16 (18)</td>
</tr>
</tbody>
</table>

Table 2. Participant’s counseling approach to a likely pathogenic variant identified in the \(CDH1\) or \(ATM\) gene

If the likely pathogenic \(CDH1\) variant was downgraded to a VUS, participants were less likely to change the management for the proband in the \(CDH1+fhx\) scenario when compared to the other two scenarios (\(p<0.001\)). A majority (28/37, 75%) of those who would change management between \(CDH1\) scenarios indicated that family history was a factor in their decision making. Although the question aimed to better understand why participants would change management for the proband, some participants specified how they would change management, such as running risk models or obtaining medical records of family members. (Supp. Fig 1D). On the other hand, participants responded similarly between the \(CDH1-fhx\) and \(ATM\) scenario (\(p>0.05\)). A summary of the pair-wise comparisons and the results of McNemar’s test can be found in Table 3.
With this specific variant downgrade scenario, does this change how you manage the proband?

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Yes, in both scenarios n(%)</th>
<th>Yes/No n(%)</th>
<th>No/Yes n(%)</th>
<th>No, in both scenarios n(%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDH1+fhx vs. CDH1-fhx</td>
<td>45 (52)</td>
<td>2 (2)</td>
<td>35 (40)</td>
<td>5 (6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CDH1+fhx vs. ATM</td>
<td>45 (52)</td>
<td>2 (2)</td>
<td>34 (39)</td>
<td>6 (7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CDH1-fhx vs. ATM</td>
<td>74 (85)</td>
<td>6 (7)</td>
<td>5 (6)</td>
<td>2 (2)</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Table 3. Pair-wise comparison of whether participants would change management between the CDH1 scenarios and ATM scenario

After the variant downgrade, a majority of counselors would discuss how the variant reclassification was reached, the possibility of another reclassification in the future, and implications for family members. There appears to be variability in the responses regarding practices in the following areas: continue recommended medical management based on guidelines, recruit family members to be in a family study, and discuss how medical management is affected by the variant downgrade (Table 4).
<table>
<thead>
<tr>
<th>Counseling approach if the likely pathogenic variant was downgraded to a VUS</th>
<th>CDH1+f hx n (%)</th>
<th>CDH1-f hx n (%)</th>
<th>ATM n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discuss how the variant reclassification was reached</td>
<td>80 (92)</td>
<td>82 (94)</td>
<td>79 (91)</td>
</tr>
<tr>
<td>Discuss the possibility of another variant reclassification in the future</td>
<td>75 (86)</td>
<td>71 (82)</td>
<td>74 (85)</td>
</tr>
<tr>
<td>Continue recommended medical management based on guidelines</td>
<td>70 (80)</td>
<td>31 (36)</td>
<td>48 (55)</td>
</tr>
<tr>
<td>Discuss implications for family members</td>
<td>81 (93)</td>
<td>81 (93)</td>
<td>72 (83)</td>
</tr>
<tr>
<td>Recruit family members to be in a family study for the specific VUS (if eligible)</td>
<td>76 (87)</td>
<td>65 (75)</td>
<td>60 (69)</td>
</tr>
<tr>
<td>Discuss how medical management is affected by the variant downgrade</td>
<td>40 (46)</td>
<td>57 (66)</td>
<td>59 (68)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (6)</td>
<td>4 (5)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

Table 4. Participant’s counseling approach to a variant downgrade scenario

To better understand the variability in responses, McNemar’s test was performed to see if participants changed their responses based on the gene or family history. Participants were more likely to continue recommended medical management based on guidelines and less likely to discuss how medical management was affected by the variant downgrade in the CDH1+f hx scenario. Along the same lines, participants were more likely to discuss recruitment of family members for family studies in the CDH1+f hx scenario compared to the CDH1-f hx and ATM scenarios (p<0.02 and p<0.002 respectively). A summary of the pair-wise comparisons and McNemar’s test can be found in Table 5.
<table>
<thead>
<tr>
<th></th>
<th>Yes, in both scenarios</th>
<th>Yes/No</th>
<th>No/Yes</th>
<th>No, in both scenarios</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n(%)</td>
<td>n(%)</td>
<td>n(%)</td>
<td>n(%)</td>
<td></td>
</tr>
<tr>
<td>Would you discuss continuation of recommended medical management based on guidelines after the variant downgrade?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$CDH1^+fhx$ vs. $CDH1^{-}fhx$</td>
<td>28 (32)</td>
<td>42 (48)</td>
<td>3 (3)</td>
<td>14 (16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$CDH1^+fhx$ vs. $ATM$</td>
<td>44 (51)</td>
<td>26 (30)</td>
<td>4 (5)</td>
<td>13 (15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$CDH1^{-}fhx$ vs. $ATM$</td>
<td>23 (26)</td>
<td>8 (9)</td>
<td>25 (29)</td>
<td>31 (36)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Would you discuss how medical management is affected by the variant downgrade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$CDH1^+fhx$ vs. $CDH1^{-}fhx$</td>
<td>37 (43)</td>
<td>3 (3)</td>
<td>20 (23)</td>
<td>27 (31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$CDH1^+fhx$ vs. $ATM$</td>
<td>35 (40)</td>
<td>5 (6)</td>
<td>24 (28)</td>
<td>23 (26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$CDH1^{-}fhx$ vs. $ATM$</td>
<td>49 (56)</td>
<td>8 (9)</td>
<td>10 (11)</td>
<td>20 (23)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Would you discuss the recruitment of family members to be in a family study of the specific VUS after the variant downgrade?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$CDH1^+fhx$ vs. $CDH1^{-}fhx$</td>
<td>61 (70)</td>
<td>15 (17)</td>
<td>4 (5)</td>
<td>7 (8)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>$CDH1^+fhx$ vs. $ATM$</td>
<td>56 (64)</td>
<td>20 (23)</td>
<td>4 (5)</td>
<td>7 (8)</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>$CDH1^{-}fhx$ vs. $ATM$</td>
<td>56 (64)</td>
<td>9 (10)</td>
<td>4 (5)</td>
<td>18 (21)</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Table 5. Pair-wise comparison of whether participants would discuss aspects of management and recruitment of family members for family studies between the $CDH1$ and $ATM$ scenarios.
Challenges Associated with Variant Downgrades

When considering challenges associated with a variant downgrade, approximately 62% (54/87) of participants characterized counseling a patient with a variant downgrade in a highly penetrant gene as difficult or very difficult. Nearly 91% (78/87) of participants perceived counseling a patient who received a prophylactic surgery before the variant downgrade occurred as difficult or very difficult. On the other hand, counseling a patient with a variant downgrade in a moderately penetrant gene and counseling the patient about how it affects the family were both characterized as neither easy nor difficult by nearly 39% (34/87) and 40% (35/87) of participants, respectively. Finally, discussing how the classification was reached (43/87, 49%) or how it affects medical management (38/87, 44%) was considered easy by most participants (Figure 4). Of the 68 participants with variant downgrade experience, a majority (36/68, 53%) experienced challenges while counseling a patient with a variant downgrade. Inductive analysis was performed on free-text responses describing those challenges and multiple prevalent themes were identified. Many participants (14/68, 21%) indicated that psychosocial concerns were a challenge. Nearly 10% (7/68) of participants noted challenges related to surgery, while 7% (5/68) encountered challenges related to family history. Another 7% (5/68) also noted challenges related to patients’ hesitations about reduced screening. Several quotes from our participants are highlighted in Figure 5.
Counseling a patient with a variant downgrade in a highly penetrant gene (i.e.-BRCA1, BRCA2, CDH1, TP53)

Counseling a patient with a variant downgrade in a moderately penetrant gene (i.e.-ATM, CHEK2)

Discussing how the classification was reached with a patient who received a variant downgrade

Discussing how a variant downgrade in a clinically actionable variant affects medical management for a patient

Counseling a patient about how the variant downgrade affects management of their family members

Counseling a variant downgrade to a patient who underwent a prophylactic surgery based on identification of a gene variant that was initially classified as pathogenic or likely pathogenic

Counseling a variant downgrade to a patient who has been receiving increased cancer screenings/surveillance based on identification of a gene variant that was initially classified as pathogenic or likely pathogenic

Figure 4. Potential challenges associated with providing genetic counseling for patients with variant downgrade
Figure 5. Summary of themes identified by qualitative inductive analysis of potential challenges presented by participant

Psychosocial concerns

- “Patient who had done a prophylactic surgery was extremely upset as this was an action that could not be reversed, she had major complications from her surgery and felt it was all for nothing”
- “When the patient’s primary feeling is of disbelief or regret. It can be difficult to ‘convince’ them of the new data.”

Challenges related to surgery

- “The most challenging scenarios are when patients have either already pursued prophylactic surgeries or are in the process of planning a procedure…”
- “It's much harder once a patient has had prophylactic surgery based on a variant downgrade.”

Challenges related to family history

- “….Patient is confused and opted to continue with increased monitoring given fhx”
- “The downgrade from P/LP to VUS is especially challenging in families where the family history appears consistent with the gene in which there is a VUS.”

Hesitations about reduced screening

- “Patients have become accustomed to their previously thought cancer risks and felt protected by the increased surveillance…. and also feel uncomfortable/worried about pulling back on cancer screening”.
- “Hesitations from patient, particularly in the setting of desiring the increased screening they have previously received”
Resources

The most common resources utilized by participants included the primary genetic testing laboratory, other genetic testing laboratories, disease databases, and other genetic counseling colleagues. This was consistent across the CDH1+/−/flx and ATM scenarios and the findings are summarized in Supplemental Material 5.

DISCUSSION

Studies in both commercial laboratory and hereditary cancer clinic settings show that only 0.3% of P/LP variants are downgraded to a VUS.\textsuperscript{10,11} Although rare, P/LP variant downgrades can pose a significant challenge for patients and their medical management.\textsuperscript{12−14} However, little is known about genetic counselors’ insights regarding these unique cases. Thus, this study sought to address the lack of knowledge in this area. Interestingly, responses from this study support that these rare cases can be difficult to navigate for genetic counselors. Participants report that it would be difficult for them to counsel a variant downgrade case, specifically if it involves a highly penetrant gene such as BRCA\textit{1} or \textit{CDH1}. Though this perception of difficulty appears to change depending on the penetrance of the gene as participants see counseling a moderately penetrant gene as neither easy nor difficult. The difference in difficulty may be attributed to the difference in management recommendations. For example, moderately penetrant genes tend to have more conservative surgery recommendations due to their relatively lower cancer risk, when compared to highly penetrant genes.\textsuperscript{6,7,18} Thus, a variant downgrade in a moderately penetrant gene may be less complicated from a surgical recommendation standpoint and may be seen as relatively easier to counsel. This is supported by our findings that nearly 91% (78/87) of participants find counseling a patient who had received a prophylactic surgery prior to the variant downgrade to be a difficult challenge. Furthermore, genetic counselors who have experience counseling patients who underwent prophylactic surgery prior to a variant downgrade pointed out that most of the difficulties stem from psychosocial concerns such as regret and uncertainty.
Similar challenges related to uncertainty can also be seen in cases involving VUS results.\textsuperscript{8,9} This is because clinical recommendations can change based on whether the VUS is reclassified to a non-actionable or actionable variant.\textsuperscript{1-3,19} As expected, a vast majority of genetic counselors practiced according to professional guidelines that recommend increased breast screening (84/87, 98\%) and option for prophylactic mastectomy (80/87, 92\%) if the VUS was reclassified to an actionable BRCA1 variant, but not if the variant was reclassified to a non-actionable variant. Participants’ responses from this study demonstrate that genetic counselors rely on patients’ personal and family histories as guides to give recommendations in the event a VUS is reclassified to a LB variant. On the other hand, when a VUS is reclassified to a P variant, then the actionability of the genetic test result is what guides medical management recommendations. Ultimately, this data supports that genetic counselors are unified in their approach to VUS reclassifications and practice according to professional guidelines. This could be attributed to genetic counselors’ experience with VUS results and the presence of professional guidelines to help manage patients identified with a VUS.

**CDH1 and ATM pre-downgrade scenarios**

Similarly, when genetic testing results are straightforward with a clear P/LP variant identified in hereditary cancer predisposition genes, it appears that genetic counselors are uniform in certain aspects, such as discussing cancer risk estimates, cancer screenings, implications for family members, and resources, regardless of the gene or family history. On the other hand, there appears to be more disagreement between participants in the practice of discussing prophylactic surgery, how the variant classification was reached, and the possibility of reclassification in the future. A minority of participants would discuss prophylactic surgery in the ATM scenario, and this is expected because there is no data to support the benefit of prophylactic surgery in these cases.\textsuperscript{7} However, the difference among participants in whether or not they discuss how the variant classification was reached and the possibility of reclassification in the future is noteworthy. As defined by ACMG/AMP guidelines, likely pathogenic implies over 90\% certainty that the variant is disease causing, rather than complete certainty. If it is the only evidence concerning of a genetic disorder, recommendations are to explain the finding carefully to
families. Furthermore, it has also been suggested that providers educate patients on the chances of a variant downgrade from an actionable variant to a non-actionable variant because of its impact on management. Participants’ hesitation to provide information about the variant classification and the chances of reclassification when cases involve LP variants suggests that these aspects are not routinely incorporated into genetic counselors’ clinical practice when an actionable result is identified.

**CDH1 and ATM post-downgrade scenarios**

Genetic counselors are united in certain areas of practice when it comes to cases involving a LP variant that was downgraded to a VUS. For these variant downgrade scenarios, it appears to be common practice for genetic counselors to discuss implications for family members, how the variant reclassification was reached, and the possibility of reclassification in the future. Additionally, genetic counselors are unified in the resources they would use in cases of variant downgrades. Prior research has explored what resources genetic counselors use for VUS results, and Scherr et. al (2015) found that genetic counselors would contact the genetic testing laboratory directly, use supplemental reports from the laboratory, discuss the results with a colleague, or search scientific literature. However, this data suggests that medical management
recommendations for a proband may be less clear when a causative variant is identified and later reclassified to a non-actionable result.

To better understand the variability observed in participants’ responses regarding patient management and recruitment of family members for family studies, further comparisons were made to see if participants altered their approach in these areas depending on the specific gene discussed or the family history. When comparing management decisions between the two CDH1 scenarios, genetic counselors were more likely to discuss aspects of management differently depending on the presence of a suggestive family history. These counseling practices are expected given that family history is an important consideration for HDGC. Under the previous HDGC guidelines published in 2015, families could have a clinical diagnosis of HDGC based on reported family history even without an identifiable CDH1 variant or with a CDH1 VUS. Based on the 2015 clinical practice guidelines, these families are still recommended to be followed by a team with expertise in HDGC and receive endoscopic surveillance. However, recent updates have differentiated HDGC as the presence of a pathogenic variant in the CDH1 gene with a reported family history of diffuse gastric cancer, while “HDGC-like” was created to encompass families who meet testing criteria for HDGC but have no identified CDH1/CTNNA1 variant. Although gastric cancer surveillance recommendations do not differ significantly between these two guidelines for patients with an identified CDH1 VUS, the updated guidelines specifically state that prophylactic gastrectomy is not advised for these individuals/families. As such, genetic counselors may have different management recommendations for the proband among the CDH1 scenarios depending on the family history presented in the scenario and/or which practice guidelines they are following. Ultimately, it appears that family history and its interpretation within professional guidelines can affect how genetic counselors counsel patients with variant downgrades from clinically actionable to non-actionable variants.

In contrast, when the CDH1 scenarios were compared to the ATM scenario, it was less certain what factors contributed to the difference in practices among genetic counselors. Participants were more likely to discuss how recommended medical management would continue based on guidelines and
recruitment of family members for family studies in the CDH1+fhx scenario. This is consistent with recommendations outlined by the HDGC clinical practice guidelines mentioned previously. Therefore, a suggestive family history could influence genetic counselors to continue recommended medical management based on guidelines and to consider family testing in other affected family members to clarify if the variant is causative. Alternatively, cancer risks associated with moderately penetrant genes, such as ATM, are relatively lower compared to highly penetrant genes. As such, individuals identified with a P/LP variant in a moderately penetrant gene could present with variable family histories. Therefore, once a LP variant in the ATM gene is downgraded to a VUS, medical management is expected to change in the absence of a family history of cancer. Still, it is unknown exactly what factors influenced genetic counselors to counsel differently between the CDH1 and ATM downgrade scenarios. Genetic counselors could have been influenced by multiple factors including, but not limited to, gene penetrance, family history, and/or availability of clinical practice guidelines. Therefore, although our study did not explicitly include questions to better understand how gene penetrance could have affected the study participants’ counseling practices in these specific variant downgrade cases, gene penetrance may have been a contributing factor in decision making.

Limitations

There are several limitations to consider in this study. First, genetic counselors with strong opinions about variant downgrade cases or who are more experienced with cases involving variant downgrades may have been more likely to respond to this survey and cause a selection bias. Furthermore, this survey was not a formally validated tool and was created by the authors which could have led some participants to interpret questions differently than intended. For example, qualitative analysis shows that some participants answered why while others answered how they would change management for a proband after a variant downgrade occurs. Given that approximately 59% of our participants had less than 5 years of experience in the cancer field and the rarity of a variant downgrade, a majority of participants were expected to have 1-5 cases at most this year and throughout their career. However, a large number of participants (18/87, 20%) indicated that they counseled 25 or more variant
downgrade cases throughout their career. Although unlikely, one possibility is that variant downgrades cases are underreported. Although variant downgrades and variant reclassifications were defined for the purposes of the survey, participants could have based their answers on their own definitions. If participants did misinterpret these definitions, genetic counselors’ experience with variant downgrade cases may be misrepresented. Lastly, this survey did not consider the recently updated HDGC guidelines, which were published shortly before distribution of the survey. Counseling approaches could have differed among participants depending on whether or not participants agree on which CDH1 scenarios met HDGC criteria. Therefore, it is possible that participants’ responses may have differed depending on which HDGC practice guidelines they are following.

**Practice Implications and Future Research**

This is the first study, to our knowledge, that describes the specific approach and practices of genetic counselors when they encounter a variant downgrade case, and the perceived and reported challenges that are associated with it. In this study, most genetic counselors characterize counseling a patient with a variant downgrade as either difficult or very difficult, especially if it involves a highly penetrant gene or a patient who received prophylactic surgery before the downgrade. There are aspects for which genetic counselors are unified in their practices with regards to variant downgrade cases. Genetic counselors seem to be exhibiting practice-based competencies outlined by ACGC which includes using pedigree analysis, inheritance patterns, genetic epidemiology, and other pertinent information to assess risk for a genetic condition. Furthermore, they are critically assessing literature and other sources of information for utilization during counseling sessions, as expected. However, it is important to note that there was relatively more discordance in how a patient was managed in these variant downgrade scenarios. Family history appears to be just one of the factors that influence genetic counselors’ approach to these cases, but gene penetrance and other factors may influence these practices as well. That being said, future research in this area can better characterize genetic counselors’ motivations behind their approach to variant downgrade cases. The variability in the patient’s management also suggests a possible need for practice guidelines to assist genetic counselors in variant
downgrade scenarios. As such, future studies should examine the desire for practice guidelines or other resources to aid genetic counselors in cases involving variant downgrades.

Another area for future research is our limited understanding of patients’ perspectives in the variant downgrade setting. To our knowledge, there is only one study that explored patients’ perspectives about reclassification, and only one of the 20 participants in the study experienced a variant downgrade. By exploring patients’ perspectives and potential needs in the variant downgrade setting, genetic counselors can gain insights from the patients’ point of view into whether there are unmet needs based on the current practicing approach or if there are any aspects of counseling that need improvement. Although this study did not explore these aspects of variant downgrades, this study contributed to the current literature regarding important considerations during variant downgrade cases. Further studies will expand our knowledge on this topic and in turn, help improve patient outcomes.
APPENDIX

Copy of Qualtrics Survey

1. Where do you currently practice as a genetic counselor?
   - United States
   - Canada
   - Other

2. How much of your time is currently dedicated to cancer genetic counseling?
   - 1-25%
   - 26-50%
   - 51-75%
   - 76-100%
   - None at all

3. What is your gender?
   - Male
   - Female
   - Other
   - Prefer not to answer

4. What is your age? ____________

5. 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

6. What is your ethnicity?
   - Hispanic
   - Non-Hispanic
   - Prefer not to answer

7. Please enter your graduation year from a genetic counseling training program.
   ____________

8. 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

9. Please select which best describes your primary place of employment (Select one):
   - University medical center
   - University/nonmedical center
10. How many years in total have you practiced as a clinical cancer genetic counselor?

________________

Definitions for the purpose of this survey

Genetic testing can identify genetic variants that are classified as benign, likely benign, variant of uncertain significance (VUS), likely pathogenic, and pathogenic.

**Variant reclassification:** A variant that is changed from one classification to another classification (i.e. – a VUS to a benign variant classification, or a pathogenic to a likely pathogenic classification).

**Variant downgrade:** A variant with a pathogenic or likely pathogenic classification that is downgraded to a lower classification (i.e. – a pathogenic to a VUS classification, or a likely pathogenic to a VUS classification)

**Actionable variants:** Pathogenic or likely pathogenic variants that can change medical management or treatment based on genetic test results (i.e. – increased cancer screening/surveillance, recommendations for preventative surgeries or targeted treatment, etc.).

**Non-actionable variants:** VUS, likely benign, or benign variants that do not change medical management or treatment (i.e. – general population cancer screening/surveillance, etc.).

11. Which of the following best represents the discussions within your department/institution regarding **variant downgrades** 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 variant downgrades in our clinics
   - Our department/institution has developed formal policies (i.e. standard of practice) regarding how to address variant downgrades in our clinics
   - Other, please specify: ___________

12. How many patients have you counseled regarding a **variant reclassification** this year?
   - 1-10
   - 11-20
   - 21-30
   - 31-40
   - 41-50
   - More than 50
   - None at all

13. How many patients have you counseled regarding a **variant downgrade** this year?
   - 1-5
   - 6-10
   - 11-15
   - 16-20
14. How many patients have you counseled regarding a **variant downgrade** over the span of your genetic counseling career?
- 1-5
- 6-10
- 11-15
- 16-20
- 21-25
- More than 25
- None at all

15. How comfortable are you counseling a patient with a **variant downgrade**? (very uncomfortable, uncomfortable, neither uncomfortable nor comfortable, comfortable, very comfortable)

You are counseling this proband. She received genetic testing from her genetic counselor 4 years ago and the results revealed a **VUS in the BRCA1 gene**. The results were **reclassified** to a **likely benign variant**.

16. Which of the following recommendations would be appropriate for the proband **based on the variant reclassification**? *Select all that apply.*
- Bilateral mastectomy
- Bilateral salpingo-oophorectomy
- Alternating breast MRI/breast mammogram every 6 months
- Consideration of serum CA-125 and transvaginal ultrasounds
- Genetic testing of the proband’s family members
- None of the above
17. Would you recommend changing the medical management for the proband’s family members based on the variant reclassification?
   o Yes. please specify: ______________
   o No. please explain: ______________

18. Which of the following factors influence your counseling in this specific variant reclassification scenario? Select all that apply.
   o The proband’s personal history
   o The proband’s family history of cancer
   o The \textit{BRCA1} likely benign variant
   o Other, please specify: ______________

Consider a different scenario for this same proband. The proband’s \textit{BRCA1} VUS was reclassified to a \textit{pathogenic variant}.

19. Which of the following recommendations would be appropriate for the proband based on the variant reclassification? Select all that apply.
   o Bilateral mastectomy
   o Bilateral salpingo-oophorectomy
   o Alternating breast MRI/breast mammogram every 6 months
   o Consideration of serum CA-125 and transvaginal ultrasounds
   o Genetic testing of the proband’s family members
   o None of the above

20. Would you recommend changing the medical management for the proband’s family members based on the variant reclassification?
   o Yes. please specify: ______________
   o No. please explain: ______________

21. Which of the following factors influence your counseling in this specific variant reclassification scenario? Select all that apply.
   o The proband’s personal history
   o The proband’s family history of cancer
   o The \textit{BRCA1} pathogenic variant
   o Other, please specify: ______________

22. How comfortable are you with disclosing \textit{CDH1} genetic test results to a patient according to each of the following results? (Very uncomfortable, uncomfortable, neither uncomfortable nor comfortable, comfortable, very comfortable)
   o Pathogenic
   o Likely pathogenic
   o Variant of unknown significance (VUS)
   o Likely benign
   o Benign

23. How comfortable are you with disclosing \textit{ATM} genetic test results to a patient according to each of the following results? (Very uncomfortable, uncomfortable, neither uncomfortable nor comfortable, comfortable, very comfortable)
   o Pathogenic
   o Likely pathogenic
   o Variant of unknown significance (VUS)
   o Likely benign
   o Benign
You are counseling this proband. The proband has no personal history of cancer. You previously ordered genetic testing for the proband due to her family history of lobular breast cancer, diffuse gastric cancer, and colon cancer. The genetic test revealed a likely pathogenic variant in the CDH1 gene. She reports a history of normal breast screenings. She has never had an Esophagogastroduodenoscopy (EGD) or any stomach biopsies. She reports no one in her family has ever undergone genetic testing. Consider the following questions and answer according to how you would approach this in your clinical practice.

24. Is the proband’s family history suggestive of Hereditary Diffuse Gastric Cancer (HDGC)?
   - Yes
   - No

25. How would you counsel the proband when genetic testing identifies a likely pathogenic variant in the CDH1 gene? Select all that apply.
   - Discuss how the likely pathogenic classification was reached (lines of evidence)
   - Discuss the possibility of variant reclassification
   - Discuss cancer risk estimates associated with a germline CDH1 likely pathogenic variant
   - Discuss implications for family members
   - Provide patient friendly resources
   - Discuss cancer screenings
   - Discuss prophylactic surgery
   - Other, please specify: ____________________

If “Discuss cancer screenings” was selected……

26. Which of the following cancer screenings would you discuss with the proband when genetic testing identifies a likely pathogenic variant in the CDH1 gene? Select all that apply.
   - Discuss breast cancer screening (clinical breast exam, annual breast mammogram or breast MRI)
   - Discuss stomach cancer screening (surveillance endoscopy with biopsy)
   - Discuss colon cancer screening (colonoscopy)
   - Other, please specify: __________
If “Discuss prophylactic surgery” was selected……

27. Which of the following cancer screenings would you discuss with the proband when genetic testing identifies a likely pathogenic variant in the \textit{CDH1} gene? \textit{Select all that apply.}
   
   - Discuss risk-reducing mastectomy
   - Discuss risk-reducing total gastrectomy
   - Other, please specify: __________

Consider a scenario where the proband’s \textit{CDH1 likely pathogenic variant} was \textbf{downgraded} to a VUS 4 years later. In that time, the proband has been receiving increased breast cancer screenings (alternating mammograms and breast MRIs every 6 months). Moreover, she underwent risk reducing total gastrectomy.

28. With this specific variant downgrade scenario, does this change how you manage the proband?
   
   - Yes. please specify: ________________
   - No. please explain: ________________

29. With this specific variant downgrade scenario, which resources would you utilize to prepare for your session? \textit{Select all that apply.}
   
   - Review primary literature
   - Gather information from primary testing laboratory on how variant reclassification was reached
   - Gather information from other genetic testing laboratories on their classification of the variant
   - Consult NSGC/Cancer SIG listservs
   - Consult other genetic counselors
   - Review databases (e.g. ClinVar, OMIM, DECIPHER)
   - Other, please specify: ________________

30. How would you counsel the proband after the likely pathogenic variant in the \textit{CDH1} gene is \textbf{downgraded} to a VUS? \textit{Select all that apply.}
   
   - Discuss how the variant reclassification was reached
   - Discuss the possibility of another variant reclassification in the future
   - Discuss that the proband and her family meet the clinical criteria for HDGC
   - Continue recommended medical management based on guidelines
   - Discuss implications for family members
   - Recruit family members to be in a family study for the specific \textit{CDH1} VUS (if eligible)
   - Discuss how medical management is affected by the variant downgrade. If so, please specify: ________________
   - Other, please specify: ________________
You are counseling this proband. The proband has no personal history of cancer. You previously ordered genetic testing for the proband due to her family history of breast cancer. The genetic test revealed a likely pathogenic variant in the CDH1 gene. She reports a history of normal breast screenings. She has never had an Esophagogastroduodenoscopy (EGD) or any stomach biopsies. She reports no one in her family has ever undergone genetic testing. Consider the following questions and answer according to how you would approach this in your clinical practice.

31. Is the proband’s family history suggestive of Hereditary Diffuse Gastric Cancer (HDGC)?
   - Yes
   - No

32. How would you counsel the proband when genetic testing identifies a likely pathogenic variant in the CDH1 gene? Select all that apply.
   - Discuss how the likely pathogenic classification was reached (lines of evidence)
   - Discuss the possibility of variant reclassification
   - Discuss cancer risk estimates associated with a germline CDH1 likely pathogenic variant
   - Discuss implications for family members
   - Provide patient friendly resources
   - Discuss cancer screenings
   - Discuss prophylactic surgery
   - Other, please specify: ________________

If “Discuss cancer screenings” was selected…….

33. Which of the following cancer screenings would you discuss with the proband when genetic testing identifies a likely pathogenic variant in the CDH1 gene? Select all that apply.
   - Discuss breast cancer screening (clinical breast exam, annual breast mammogram or breast MRI)
   - Discuss stomach cancer screening (surveillance endoscopy with biopsy)
   - Discuss colon cancer screening (colonoscopy)
   - Other, please specify: __________
If “Discuss prophylactic surgery” was selected……

34. Which of the following cancer screenings would you discuss with the proband when genetic testing identifies a likely pathogenic variant in the CDH1 gene? *Select all that apply.*
  - Discuss risk-reducing mastectomy
  - Discuss risk-reducing total gastrectomy
  - Other, please specify: __________

Consider a scenario where the proband’s *CDH1 likely pathogenic variant* was *downgraded* to a VUS 4 years later. In that time, the proband has been receiving increased breast cancer screenings (alternating mammograms and breast MRIs every 6 months). Moreover, she underwent risk reducing gastrectomy.

35. With this specific variant downgrade scenario, does this change how you manage the proband?
  - Yes. please specify: ______________
  - No. please explain: ______________

36. With this specific variant downgrade scenario, which resources would you utilize to prepare for your session? *Select all that apply.*
  - Review primary literature
  - Gather information from primary testing laboratory on how variant reclassification was reached
  - Gather information from other genetic testing laboratories on their classification of the variant
  - Consult NSGC/Cancer SIG listservs
  - Consult other genetic counselors
  - Review disease databases (e.g. ClinVar, OMIM, DECIPHER)
  - Other, please specify: ______________

37. How would you counsel the proband *after* the likely pathogenic variant in the *CDH1 gene is downgraded* to a VUS? Select all that apply. *Select all that apply.*
  - Discuss how the variant reclassification was reached
  - Discuss the possibility of another variant reclassification in the future
  - Discuss that the proband and her family meet the clinical criteria for HDGC
  - Continue recommended medical management based on guidelines
  - Discuss implications for family members
  - Recruit family members to be in a family study for the specific *CDH1 VUS* (if eligible)
  - Discuss how medical management is affected by the variant downgrade. If so, please specify: ______________
  - Other, please specify: _______________
You are counseling this proband. The proband has no personal history of cancer. You previously ordered genetic testing for the proband due to her paternal aunt’s history of breast cancer. The genetic test revealed a **likely pathogenic variant** in the *ATM* gene. The proband reports a history of normal breast screenings. She reports no one in her family has ever undergone genetic testing. Consider the following questions and answer according to how you would approach this in your clinical practice.

38. In this scenario, what recommendations would be appropriate for the proband? *Select all that apply.*
   - Breast MRI/mammogram every 6 months
   - Risk reducing mastectomy
   - I would not recommend increased cancer screening surveillance/risk reducing surgeries to the proband

39. How would you counsel the proband when genetic testing identifies a **likely pathogenic variant in the *ATM* gene**? *Select all that apply.*
   - Discuss how the likely pathogenic classification was reached (lines of evidence)
   - Discuss the possibility of variant reclassification
   - Discuss cancer risk estimates associated with a germline *ATM* likely pathogenic variant
   - Discuss implications for family members
   - Provide patient friendly resources
   - Discuss cancer screenings. If so, please specify: __________
   - Discuss prophylactic surgery. If so, please specify: __________
   - Other, please specify: __________

Consider a scenario where the proband’s *ATM likely pathogenic variant* was **reclassified** to a VUS 4 years later. In that time, the proband underwent increased breast cancer screening surveillance.

40. With this specific variant downgrade scenario, does this change how you manage the proband?
   - Yes. please specify: __________
   - No. please explain: __________
41. With this specific variant downgrade scenario, which resources would you utilize to prepare for your session? Select all that apply.
   o Review primary literature
   o Gather information from testing laboratory on how variant reclassification was reached
   o Gather information from other genetic testing laboratories on their classification of the variant
   o Consult NSGC/Cancer SIG listservs
   o Consult other genetic counselors
   o Review disease databases (e.g. ClinVar, OMIM, DECIPHER)
   o Other, please specify: _________________

42. How would you counsel the proband after the likely pathogenic variant in the ATM gene is \textit{downgraded} to a VUS? Select all that apply.
   o Discuss how the variant reclassification was reached
   o Discuss the possibility of another variant reclassification in the future
   o Continue recommended medical management based on guidelines
   o Discuss implications for family members
   o Recruit family members to be in a family study for the specific ATM VUS (if eligible)
   o Discuss how medical management is affected by the variant downgrade. If so, please specify: _________________
   o Other, please specify: _________________

Please indicate how easy or difficult you find the following scenarios involved in counseling a \textbf{variant downgrade} \textit{Very easy, easy, neutral, difficult, very difficult)}

43. Counseling a patient with a variant downgrade in a highly penetrant gene. (i.e.-\textit{BRCA1, BRCA2, TP53, CDH1})

44. Counseling a patient with a variant downgrade in a moderately penetrant gene. (i.e.-\textit{ATM, CHEK2})

45. Discussing how the classification was reached with a patient who received a variant downgrade.

46. Discussing how a variant downgrade in a clinically actionable variant affects medical management.

47. Counseling a variant downgrade to a patient who underwent a prophylactic surgery based on identification of a gene variant that was initially classified as pathogenic or likely pathogenic.

48. Counseling a variant downgrade to a patient who has been receiving increased cancer screenings/surveillance based on identification of a gene variant that was initially classified as pathogenic or likely pathogenic.

49. Counseling a patient about how the variant downgrade affects management of their family members.

50. Did you experience any challenges when counseling a patient about variant downgrades?
   o Yes \rightarrow Please explain
   o No

51. What resources did you find helpful as you counseled your patient(s) about variant downgrades? \textit{(free response)}
52. Please enter your e-mail address if you wish to be entered into the drawing for one of two $50 Amazon gift cards.

<table>
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<th>Would you recommend changing the medical management for the proband’s family members based on the variant reclassification?</th>
<th>Yes, in both scenarios</th>
<th>Yes/No</th>
<th>No/Yes</th>
<th>No, in both scenarios</th>
<th>p-value</th>
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<td>6 (7)</td>
<td>77 (84)</td>
<td>0(0)</td>
<td>4 (5)</td>
<td>&lt;0.001</td>
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**Supplementary Table 1.** Pair-wise comparison of whether participants would change the medical management for the proband’s family in the BRCA1 reclassification scenario

**Supplementary Figure 1.** Factors that influenced counseling in the BRCA1 reclassification scenarios
Supplementary Figure 2. Resources utilized by genetic counselors during variant downgrade case.


VITA

Grant William Bonesteel was born in California, the son of Jeannine Nance and Phillip Bonesteel. After completing his work at Foothill High School, Tustin, California in 2010, he entered the University of Colorado, Boulder, Colorado. He received the degree of Bachelor of Arts with a major in biochemistry and molecular, cell, and developmental biology in May 2015. For the next 4 years, he worked as a research assistant at the California Institute of Technology and University of California, Irvine. In August 2019, he entered The University of Texas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences.

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