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The Perspectives of Emerging Adults with Hereditary Diffuse Gastric Cancer

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THE PERSPECTIVES OF EMERGING ADULTS WITH HEREDITARY DIFFUSE GASTRIC CANCER

by

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ABSTRACT

Individuals with hereditary diffuse gastric cancer (HDGC) caused by a *CDH1* mutation have a high lifetime risk of developing gastric cancer. National guidelines recommend *CDH1* carriers undergo a prophylactic total gastrectomy (PTG)— a surgery that greatly reduces the risk of developing gastric cancer but has significant co-morbidities. This study explores the impact of a diagnosis of HDGC in the transitional life stage between the ages of 18-29 deemed "emerging adulthood." We surveyed 21 *CDH1* carriers and conducted semi-structured phone interviews with 6 *CDH1* carriers between the ages of 18-29 to learn about their life experiences regarding education, career, relationships, and family planning. Participants were also asked about their experience with genetic counseling. Specific challenges that were highlighted by participants included time away from work due to doctors' appointments and surgery recovery, an impact on relationships with family and friends, and difficult choices regarding family planning. Participants also struggle with the burden of being the expert on their condition in relation to their friends and healthcare providers, though they find support and knowledge in online groups for HDGC. These results demonstrate the challenges of an HDGC diagnosis during emerging adulthood. Practice recommendations for genetic counselors include providing HDGC-specific information for anticipatory guidance, family planning options, and psychological health.

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LITERATURE REVIEW

1.1 Hereditary Diffuse Gastric Cancer

Gastric cancer is the fifth most prevalent and the third leading cause of cancer-related death worldwide (Ferlay et al., 2012). While most gastric cancer is sporadic, familial clustering is observed in 10% of cases, with 1-3% arising from known germline mutations (van der Post et al., 2015). Hereditary diffuse gastric cancer (HDGC) is an autosomal dominant cancer predisposition syndrome characterized by the development of early-onset diffuse gastric cancer. HDGC is caused by germline, pathogenic mutations in the tumor suppressor gene *CDH1*, located on chromosome 16. *CDH1* encodes E-cadherin, an intercellular adhesion glycoprotein that plays an essential role in epithelial differentiation. A founder mutation in *CDH1* was first identified in the Maöri population of New Zealand in 1998 (Guilford et al., 1998). Since then, approximately 155 pathogenic germline mutations have been reported (van der Post et al., 2015). Most pathogenic mutations in *CDH1* lead to a non-functional protein product, resulting in loss of cellular growth control and increased invasiveness into surrounding tissues (Fitzgerald et al., 2010). HDGC is the only known cancer syndrome that is dominated by gastric adenocarcinoma, though gastric cancer is indicated in other hereditary cancer syndromes such as Li Fraumeni and Peutz-Jeghers (Guilford, Humar, & Blair, 2010; van der Post et al., 2015). The lifetime risk of gastric cancer in these syndromes is variable but consistently lower than that of HDGC (van der Post et al., 2015).

The majority of gastric adenocarcinomas can be classified into one of two categories: intestinal-type or diffuse-type. Intestinal-type adenocarcinomas are more common in older patients and are associated with environmental factors such as *H. pylori* infection. Globally, intestinal-type gastric cancers are on the decline, while diffuse-type are on the rise (Pernot et al., 2015). Currently, diffuse-type adenocarcinomas, as seen in HDGC, account for 35% of all stomach cancer diagnoses and are typically earlier-onset. These cells are poorly differentiated and infiltrate nearby structures, spreading under histologically normal-looking mucosa and causing linitis plastica, or thickening of the wall. This type of cancer does not form a distinct mass, unlike intestinal-type gastric cancer (Schneider, 2012). The accumulation of intracellular mucin pushes the nucleus aside in these cells, causing a "signet ring" appearance. As such, this type of diffuse gastric cancer is often referred to as signet ring cell carcinoma (SRCC). SRCC is a more aggressive type of cancer and is associated with poorer outcomes (Volegaar et al., 2017).

1.2 Surveillance Guidelines and Recommendations

HDGC is highly penetrant, with a 70% risk of diffuse gastric cancer for men and a 56% risk for women by age 80. Women carry an additional 42% cumulative risk for lobular breast cancer, compared to the typical lifetime risk of 12% (Hansford, Kaurah, & Li-Chang, 2015). While surveillance by upper endoscopy is an option for *CDH1* mutation carriers, the earliest signs of diffuse gastric cancer are subtle changes of the stomach wall, which are commonly missed (Schneider, 2012). Hebbard et al. (2009) retrospectively analyzed pre- and post-PTG biopsies in 23 patients. While diffuse SRCC were found in only 2 patients by upper endoscopy prior to surgery, final pathological evaluation post-surgery revealed SRCC in all but one patient (96%). Lynch et al. (2008) found that 10 of

11 patients in their cohort who underwent PTG had occult carcinomas upon examination of post-TG specimen. Six of these patients had undergone chromoendoscopy, endoscopic ultrasound, random biopsies, and PET-CT scanning prior to surgery.

The identification of multiple small foci of SRCC in almost all *CDH1* carriers, including those in their teenage years, complicates the practicality of endoscopy for patients. The average age of diagnosis of diffuse gastric cancer in HDGC patients is 38, suggesting a prolonged latent phase before invasion of the submucosa. However, the duration of this latent phase remains unpredictable and varies widely even within families (Blair et al., 2006). As such, *CDH1* carriers are advised to undergo a prophylactic total gastrectomy (PTG) in their early twenties (van der Post et al., 2015).

1.3 Genetic Testing

According to National Comprehensive Cancer Network guidelines, one of the following criteria qualifies an individual for a clinical diagnosis of HDGC, in addition to genetic testing for pathogenic mutations in the *CDH1* gene:

1) Two gastric cancer cases in a family, with one confirmed diffuse gastric cancer diagnosed under 50 years;

2) Three confirmed cases of diffuse gastric cancer in first- or second-degree relatives independent of age;

3) Diffuse gastric cancer diagnosed before age 40 without a family history;

4) A personal or family history of diffuse gastric cancer and lobular breast cancer, with one diagnosis under 50 (NCCN, 2018).

While a confirmed pathogenic mutation in the *CDH1* gene is effectively a diagnosis of HDGC, not having a mutation does not rule out a diagnosis based on personal and family

history. In fact, the majority of individuals with a diagnosis of HDGC do not have an identifiable genetic cause, as only 40% of families meeting testing criteria have a germline *CDH1* mutation. The genetic basis for the remaining cases of familial gastric cancers are unknown, but likely involves mutations in other genes not yet identified (Hansford et al., 2015). Mutations in *MAP3K6* have also been implicated in families with a strong history of gastric cancer, but its pathogenicity is questionable due to incomplete variant segregation with disease and a high population frequency in databases like ExAc (Volegaar et al., 2017). Several families meeting HDGC criteria have been found to have pathogenic mutations in *CTNNA1*, which is in the same pathway as *CDH1* (Volegaar et al., 2017).

A new subsection of individuals without a family history of gastric cancer are discovering their *CDH1* mutations after undergoing multi-gene panel testing. Cancer genetic testing has shifted drastically over the past several years, from targeted testing of *BRCA1* and *BRCA2* alone, to testing large panels of genes associated with many different types of cancer, including *CDH1*. These "incidental findings" of *CDH1* mutation carriers call into question the penetrance and cancer risks typically quoted, which were originally calculated from families with a strong history of gastric cancer. Due to the rarity of the condition, management recommendations are drawn from a limited number of patients. A recent study sought to resolve this confusion by comparing patients with a *CDH1* mutation undergoing PTG who met or did not meet testing criteria, finding that all patients had early signs of gastric cancer regardless (Lowstuter et al., 2018).

1.4 Total Gastrectomy

Patients who elect surgical intervention typically undergo a total gastrectomy with esophagojejunal anastomosis and Roux-en-Y reconstruction. The esophagus is resected above the gastro-esophageal junction and later reconnected to the small intestine after removal of the stomach. Patients can still eat and drink, but typically eat smaller portions throughout the day rather than the typical three meals. Depending on the surgical center, patients also have the option of minimally invasive laparoscopic-approach as opposed to a traditional open surgery (Strong et al., 2017).

Total gastrectomy is a major surgery, with physiological and psychological recovery estimated to take approximately one year and additional complications continuing throughout the rest of life (van der Kaaij et al., 2018). Strong et al. (2018) reported postsurgical outcomes for 41 patients with a *CDH1* mutation who underwent PTG, finding a median length of hospital of seven days, with a range of four to 50. Virtually all patients experienced substantial weight loss—about 15% of preoperative weight—and 27% of patients had a complication requiring intervention. Pulmonary complications, wound infections, and anastomotic leaks were also common. Despite the common sequelae of surgery, almost all patients ultimately reported their overall outcome "as expected" or "better than expected" (Strong et al. 2018).

Kaaij et al. (2018) also reported outcomes of PTG for 26 patients, finding that postoperative complications occurred in 31% of patients, with 19% requiring surgical re-intervention. Several patients were also readmitted to the hospital for nutritional and/or psychosocial support within a year after PTG. Most individuals experienced dumping syndrome post-surgery, which is caused by rapid entry of food into the small intestine

and results in nausea, abdominal pain, diarrhea, and vomiting. For many patients, dumping syndrome persists well after the estimated one-year recovery mark, in addition to bile reflux and the use of pancreatic enzyme supplements. The rapid rise and then rapid decrease of blood sugar can also cause weakness, sweating, and fatigue. Because food bypasses the major sites for calcium, vitamin D, iron, and folate absorption in the duodenum and jejunum, patients are at an increased risk of malnutrition, osteoporosis and osteomalacia (Guilford et al., 2010).

1.5 The Psychosocial Impact

At-risk individuals are faced with difficult decisions about if and when to undergo a prophylactic total gastrectomy, balancing the chance they may never develop cancer with the limitations of endoscopic surveillance. Many have reported delaying the surgery due to the complications such as weight loss, iron deficiency anemia, osteoporosis, and rapid intestinal transit causing dumping syndrome (Muir et al., 2016). The psychological impact of decisions regarding a prophylactic total gastrectomy is substantial.

Hallowell et al. (2016) interviewed individuals with HDGC about their decision-making process regarding a prophylactic total gastrectomy (PTG), finding that for some individuals, coming to a decision about if and when to undergo surgery was difficult. Uncertainty about the future and the development of cancer led some individuals to elect for the PTG, while others felt the uncertainty influenced their decision to postpone surgery until a positive biopsy result. Ultimately, individuals with HDGC are influenced by multitude of factors in regard to their cancer surveillance, including objective confirmation of cancer by positive biopsy, familial cancer burden, perceptions of post-

surgical life, concerns that surveillance could miss a cancer developing, and the individual's life stage (Hallowell et al., 2016).

In the same study, Hallowell et al. (2017b) interviewed patients who had undergone PTG and found that most reported surgery and recovery was easier than anticipated, with younger patients reporting faster recovery times. However, many struggled with body image issues and changing social, familial, and romantic relationships in the aftermath of the surgery. These individuals reported feeling isolated due to not being able to go out to eat or drink with friends, in addition to chronic fatigue and a negative impact on sexuality. Ultimately, all interviewees viewed the benefits of the risk reduction as outweighing the cost of surgery, but not without serious drawbacks (Hallowell et al., 2017b).

Muir et al. (2016) also assessed overall well-being in patients who had undergone PTG before and after their surgery, including standardized measures of health-related quality of life (HRQOL), body image, psychological distress, regret, and decisional conflict. Patients reported pain, fatigue, nausea, insomnia, dyspnea, and appetite loss two weeks post-operation and did not reach baseline until one year after surgery. Notably, half of patients expressed regret over having the surgery four weeks post-operation, but this decreased to near zero over time. Most patients did not experience a substantial change in body image and reported few symptoms of psychological distress. The most pressing concern for the majority of patients was the drastic weight loss (Muir et al., 2016).

1.6 Emerging Adulthood

In the past, the transition between adolescence and adulthood was brief. Many people entered the workforce immediately after finishing school, with marriage and childbearing occurring shortly thereafter (Arnett, 2000). Widespread cultural shifts over the past half-century have stretched this timeline for the majority of Americans. The US Census Bureau reports the average age of first marriage for women and men respectively has jumped from 21 and 23 in 1950, to 28 and 30 in 2018 (US Census Bureau, 2018). In addition, the percentage of Americans with a bachelor's degree or higher has increased from less than 5% in 1940 to over 33% in 2016. The concept of a new, distinct life stage between adolescence and young adulthood, deemed "emerging adulthood," was proposed by psychologist Jeffrey Arnett in 2000. Emerging adulthood spans the late teens through the twenties and is characterized as a period of change and exploration of possible life directions, before making enduring life decisions.

While it is widely recognized that the needs of children and adolescents vary from adults in regard to healthcare and psychosocial support, the differing needs of emerging adults is largely unrecognized. Epidemiologic studies have shown that 40% of emerging adults in the USA meet criteria for a psychiatric disorder (e.g. anxiety and substance misuse disorders), which is higher than every other age range (Arnett et al., 2014). For emerging adults with a mental illness, receiving a diagnosis can contrast the individual's perception of their identity and reinforces a sense of abnormality (Arnett et al., 2014). Similarly, individuals with HDGC may also struggle to cope with their cancer experience during this unique period of identity exploration and instability.

While no studies have specifically assessed emerging adults in regard to hereditary diffuse gastric cancer, comparable studies have been done with another hereditary cancer syndrome, Familial Adenomatous Polyposis (FAP). FAP is analogous to HDGC in that it is a rare and highly penetrant hereditary cancer syndrome, typically requiring prophylactic removal of the colon in adolescence or early adulthood. Mireskandari et al. explored the psychosocial impact of FAP amongst 18- to 35-year-olds by conducting in-depth interviews and found that the emerging adult population had specific psychosocial needs and areas of concern. Participants disclosed numerous issues regarding how FAP has impacted their life, including struggling with body image and physical functioning as a result of surgery, anxiety about discussing FAP with new partners, issues in relation to family planning, and a negative impact on employment. The study concluded that longer-term support appears to be essential for this group of young adults (Mireskandari et al., 2009).

Individuals with HDGC also face difficult decisions regarding planning a family. As an autosomal dominant condition, there is a 50% chance for each pregnancy to be affected. A study by Hallowell et al. explored the perceptions of individuals with HDGC regarding reproductive decisions and family planning. Participant ages ranged from 19-77, with a mean age of 40. Individuals who had completed childbearing prior to receiving a diagnosis of HDGC expressed relief that they had not needed to consider this condition prior to having children, as it may have affected the way in which they structured their family. Regarding reproductive technology, the majority of interviewees were not in favor of using prenatal diagnosis and subsequent termination of pregnancy. Many were in favor of using pre-implantation genetic diagnosis to screen embryos, but voiced concerns

about the cost and fail rate of in-vitro fertilization. Several participants anticipated difficulty in communicating information about HDGC and about their risk to future partners (Hallowell et al., 2017a).

Emerging adults with HDGC face numerous challenges, including the high risk of developing cancer, invasive cancer surveillance measures, decision-making about a major surgery with long-term complications, and the pain related to having relatives affected with cancer and possible subsequent deaths. Evidence shows that young people are at elevated risk of poor psychological adaptation to hereditary cancer syndromes, and emerging adults with HDGC may have unique needs regarding psychosocial support (Mireskandari et al., 2009). This study aims to explore the perspectives and experiences of emerging adults to better characterize and identify unmet needs so that their healthcare providers can better support them.

CHAPTER 2

THE PERSPECTIVES OF EMERGING ADULTS WITH HEREDITARY DIFFUSE GASTRIC CANCER[1]

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2.1 Abstract

Individuals with hereditary diffuse gastric cancer (HDGC) caused by a *CDH1* mutation have a high lifetime risk of developing gastric cancer. National guidelines recommend *CDH1* carriers undergo a prophylactic total gastrectomy (PTG)— a surgery that greatly reduces the risk of developing gastric cancer but has significant co-morbidities. This study explores the impact of a diagnosis of HDGC in the transitional life stage between the ages of 18-29 deemed "emerging adulthood." We surveyed 21 *CDH1* carriers and conducted semi-structured phone interviews with 6 *CDH1* carriers between the ages of 18-29 to learn about their life experiences regarding education, career, relationships, and family planning. Participants were also asked about their experience with genetic counseling. Specific challenges that were highlighted by participants included time away from work due to doctors' appointments and surgery recovery, an impact on relationships with family and friends, and difficult choices regarding family planning. Participants also struggle with the burden of being the expert on their condition in relation to their friends and healthcare providers, though they find support and knowledge in online groups for HDGC. These results demonstrate the challenges of an HDGC diagnosis during emerging adulthood. Practice recommendations for genetic counselors include providing HDGC-specific information for anticipatory guidance, family planning options, and psychological health.

2.2 Introduction

Hereditary diffuse gastric cancer (HDGC) is a cancer predisposition syndrome that confers up to a 70% and 56% lifetime risk of developing diffuse gastric cancer for men and women respectively. HDGC is attributable to mutations in the E-cadherin gene

(*CDH1*), which encodes epithelial cell adhesion proteins. Diffuse-type adenocarcinomas are poorly differentiated and spread under histologically normal-looking mucosa without forming a distinct mass, rendering endoscopic surveillance largely ineffective at detecting this type of cancer in its early stages (van der Post et al., 2015). Many gastric cancers in individuals with HDGC are diagnosed under age 40, with some occurring as young as the mid-teens (Lynch et al., 2008). As such, *CDH1* carriers are advised to undergo prophylactic total gastrectomy (PTG) in their early to mid-20s—a key portion of a newly recognized life stage deemed "emerging adulthood." This time period between the ages of 18 to 29 is marked by tremendous transition and growth (Arnett, 2000). As at-risk individuals navigate completing their education, beginning a career and starting families, they must also decide if and when to undergo PTG— recovery from which can take up to a year or longer. As such, the physical and psychosocial burden of a diagnosis of HDGC has significant implications for emerging adults, likely affecting areas of life including education, employment, familial and romantic relationships, and family planning.

This study aims to explore the impact of this hereditary cancer syndrome during a time of exploration and rapid transition through which emerging adults shape their lives. A need exists for expansion upon previous studies on the psychosocial impact and decision-making factors regarding the prophylactic total gastrectomy by assessing HDGC in a broader context, including domains of life not limited to the surgery. Regarding family planning, this study will assess similar perceptions as the Hallowell 2017a study, while focusing specifically on the concerns of emerging adults, likely prior to starting a family. In all, this study will explore the impact of HDGC regarding education, employment, relationships, and family planning. To our knowledge, no other studies have

addressed these themes in this population. The information gained from this study will identify specific areas in which emerging adults with HDGC need support and provide context to emerging adults' decision-making regarding cancer management. Awareness of the particular difficulties these individuals face may better prepare genetic counselors and other healthcare professionals to identify these struggles and address unmet needs.

2.3 Materials and Methods

Participants

Participants included individuals between the ages of 18-29 with an identified *CDH1* mutation. Participants outside of this age range, in addition to participants who had not had genetic testing or had received a Variant of Uncertain Significance, were excluded from the study. Participants were recruited via an advertisement on the No Stomach For Cancer Facebook page and other Facebook support groups. The advertisement included a description of the study and a link to the confidential online questionnaire. Participation was voluntary and respondents were not given any compensation. The University of South Carolina Institutional Review Board (IRB) deemed this study exempt from review in June 2018.

Materials/Measures

This study utilized mixed methodology consisting of a questionnaire and a semi-structured interview. Mixed methods provided a comprehensive and more complete understanding of each individual's experience, with generalized data being collected from the questionnaire and in-depth experiences gained from the interviews. The online questionnaire contained questions about demographics, personal and family history of cancer, and surgery status, in addition to experiences regarding education, career,

relationships, family planning, and genetic counseling. The questionnaire was comprised of multiple choice, Likert scale, and open-ended text entry questions. The semi-structured interviews were conducted over the phone by a single researcher and included similar themes as the online questionnaire. Additionally, phone interviewees were asked about the impact on their overall life plans, their feelings upon diagnosis, and what information they would like medical professionals and newly diagnosed HDGC patients to know.

Procedure

The questionnaire (Appendix B) was administered online through Survey Monkey. The introduction to the questionnaire outlined the goals of the study and participants gave their consent to participate by clicking "yes" to the first question. Participants were able to skip any question or leave the questionnaire at any time. Because participants were able to skip questions, there is variation in response rate. On average, respondents spent 13 minutes completing the questionnaire. Upon completion, respondents had the option to provide their contact information for a semi-structured telephone interview. The principal investigator (PI) contacted interested participants via email to determine a time for the interview. Verbal consent for participation was obtained at the beginning of each interview (Appendix C). On average, the interviews lasted 25 minutes (range 12-45 minutes). Interviews were recorded on the PI's password protected computer and transcribed verbatim.

Quantitative data were analyzed using SPSS statistical analysis software. Analyses via descriptive statistics, reliability, and correlations were conducted as appropriate. We analyzed the perceived impact of HDGC on education, career, relationships, and family planning. The level of impact was assessed using a Likert scale

(1=strongly disagree; 5=strongly agree) and were represented with descriptive statistics (percentages and means). Qualitative thematic analysis was utilized to identify and analyze reporting patterns within responses from open-text entry questions and semi-structured interviews (Mays & Pope, 2000). After the raw data was read several times, emergent themes were developed and grouped into categories based on their similarities. Responses relevant to each category were examined using constant comparison, a process in which each item is compared with the rest of the data to establish analytical categories. Categories were added as needed to reflect the nuances of the data. Quotations were extracted and classified to their corresponding theme and reported on their frequency. Data was collected from September 2018 to January 2019.

2.4 Results

In all, 28 participants completed the online questionnaire and seven respondents were excluded based on age or genetic testing status. Of the 21 eligible respondents, 16 (76.2%) were female, four (19.1%) were male, and one individual (4.8%) identified as non-binary. The median age range of the participants was 24-26 years. Most (95.2%) participants identified as Non-Hispanic White and one individual (4.8%) as Hispanic/Latino. The majority (61.9%) of participants reside in the US, with some (38.1%) participants residing outside the US in Canada and Europe (Appendix A). Six participants also completed a follow-up telephone interview. Direct quotes are copied verbatim from the open-text entry unless otherwise indicated to be from a telephone interview.

Participants identified their *CDH1* mutation status between the ages of 17-27, with a median age of 21. Approximately one-third (33.3%) of participants indicated that

they have had stage 1 stomach cancer cells on screening, eight (38.1%) had not, one (4.8%) did not know, and five (23.8%) had not had any screening. Roughly half (47.6%) of participants had their stomach surgically removed. Those who had their stomach removed did so between the ages of 21-28, with a median age of 24.5. All participants have a known family member with a *CDH1* mutation. Almost all (95.2%) participants reported they have a known family member with a *CDH1* mutation who has had cancer in the past. The most frequently reported type of cancer for these family members was stomach, followed by breast and colon.

Education

Participant education level ranged from completion of high school to completed master's degree. The majority (71.4%) of participants continued their education beyond high school (Appendix A). Participants ranked their level of agreement with different statements addressing the impact HDGC has had on six aspects of their education. Participants were most impacted in "the timing in which I pursued my education" and "impacted what I chose to study" (mean=2.8; Figure 2.1). Several participants noted in the open text-entry that they had completed their education prior to finding out their mutation status or prior to pursuing PTG. Several respondents did note the need to take time off school due to endoscopy screening procedures and impending surgeries. In contrast, some respondents felt having HDGC has had a positive impact on their educational goals, specifically in regards to pursuing a career in medicine:

> "I found out about the CDH1 mutation and the resulting signet ring cells during my A-levels; this severely affected my mental health and in turn affected my A-level grades. I then took 2 gap years, before going to uni, to work on my mental health… I now study BSc Biomedical Science and wish to pursue a career in cancer research, particularly in digestive cancers. I am thriving at uni, gaining

> high 1sts in all modules and it is the motivation gained from my own experience that is driving this." — 21-23 y.o female (participant 1)
>
> "It has interested me in other areas of medicine I had not considered and strengthened my desire to go to medical school." — 21-23 y.o. female (participant 16)
>
> "I am a nursing student currently in school and am continuing my education through the surgery and process. It makes me more motivated in ways but is obviously hard knowing I have appointments and a large surgery." — 21-23 y.o. female (participant 9)

Career

Almost half of respondents are currently working in their career field (47.6%), while others are currently working, but in a field they consider temporary (14.3%). For reasons unrelated to HDGC, 28.6% of individuals report not working. The questionnaire asked participants to rate their level of agreement with different statements addressing the impact HDGC has had on six aspects of their career. Participants were most impacted in "caused me to take off work" (mean=3.7; Figure 1.2). Approximately one-third of participants (31.6%) felt that HDGC had influenced their choice of career and 45% agreed that HDGC affected their job performance. Over half (52.6%) of participants agreed that they had taken time off work for HDGC-related reasons. In the open-ended text entry, several participants cited negative impacts on their career in regards to PTG and recovery:

> "I'm currently in training for a new career and awaiting surgery so it will impact my career drastically as I will be needing time off and will not be eligible for benefits as a new employee." — 24-26 y.o. female (participant 14)
>
> "It was a full 6 months before I was physically ready to step back into a part time position. Now at a year post I'm working full time and feel strong. My several month hiatus definitely impacted my position, job, and relevance in a small growing company." — 27-29 y.o. male (participant 4)

> "I'm self employed - but have reduced my working hours to recover. I feel that eating is a full time job and my day revolves around that." — 27-29 y.o. female (participant 18)

Other participants felt that HDGC has not negatively affected their career and, in some cases, motivated them more:

> "I have had to take time off to attend testing and treatment. But other than that I don't feel it has affected my work." — 27-29 y.o. female (participant 20)

> "Although I have to take frequent time off work for surveillance endoscopies, having HDGC does not affect my work in a negative way. It is only making me want to work harder to be able to get to where I want to be for my future career: in cancer research." — 21-23 y.o. female (participant 1)

Relationships with romantic partners, family, and friends

In regards to romantic relationships, participants were either single (23.8%), in a committed relationship (28.6%), or married (33.3%). The questionnaire asked participants to rate their level of agreement with different statements addressing the impact HDGC has had on six aspects of their romantic relationships. Overall, participants disagreed with the idea that HDGC impacted their romantic relationships. The statement that most closely approached "neither agree nor disagree" was in regard to "going out on dates and other social activities" (mean=2.6; Figure 2.3). Many respondents in committed relationships or married found their partners to be a source of support. Several single respondents had concerns about meeting potential partners, especially related to PTG:

> "I have been nervous about dating and seeking out partners since my surgeries (mastectomy and TG)." — 21-23 y.o. female (participant 16)

> "It hasn't impacted it through diagnosis only but I anticipate it affecting relationships after surgery." — 24-26 y.o. female (participant 14)

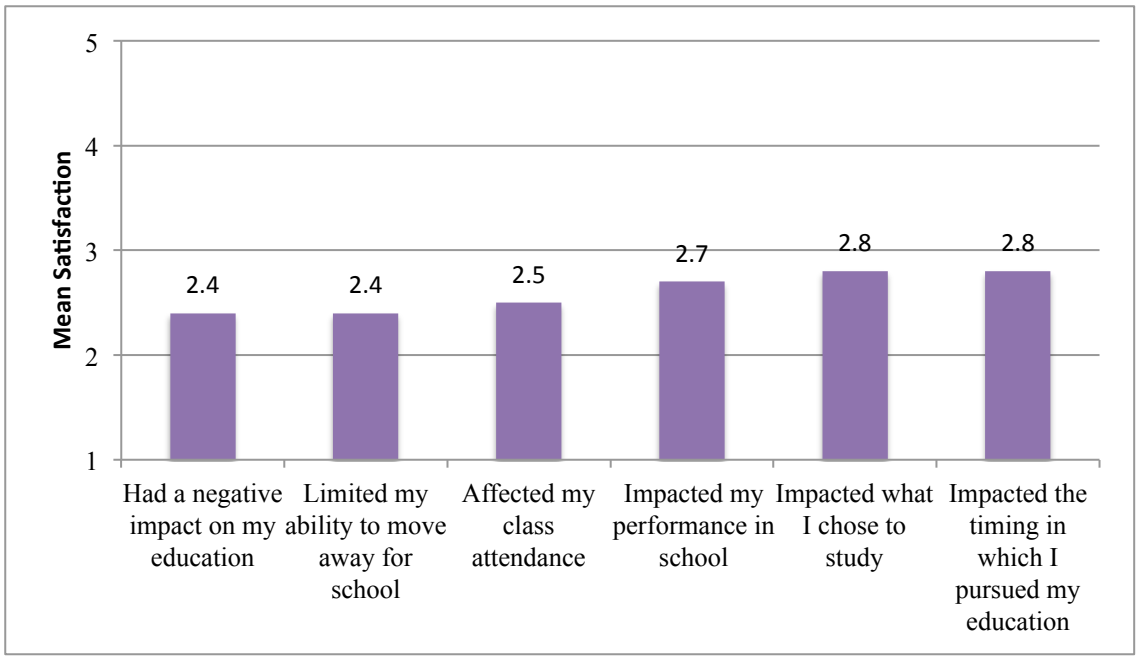

Figure 2.1 Impact on Education. Participants' perceptions of the level of impact HDGC has had on their education (1=strongly disagree; 5=strongly agree).

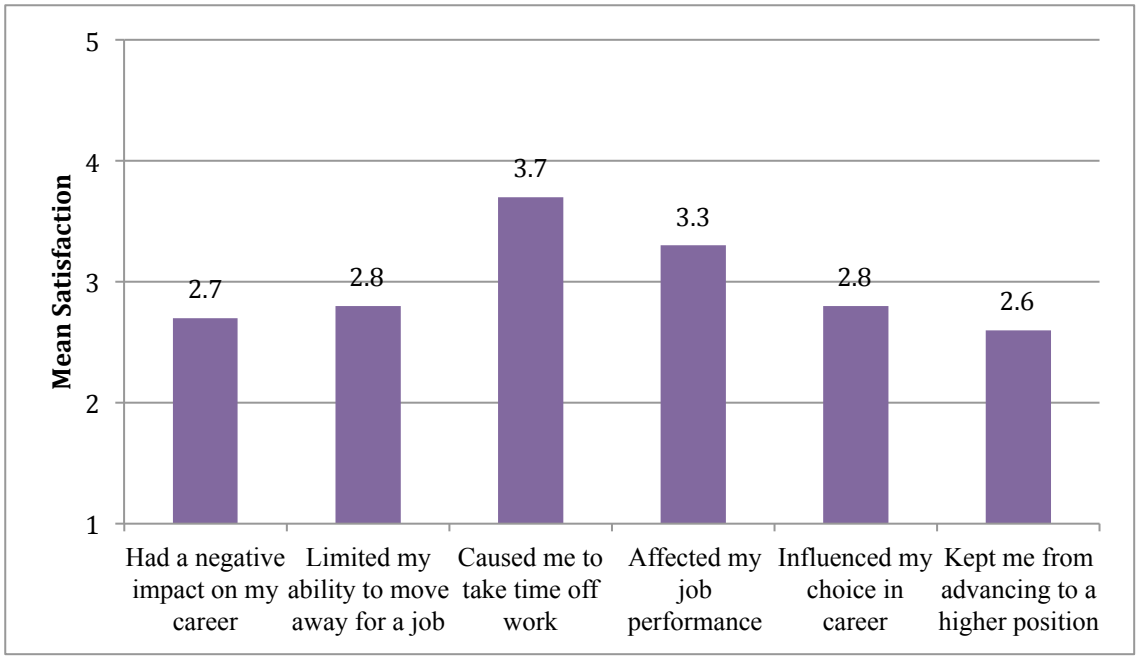

Figure 2.2 Impact on Career. Participants' perceptions of the level of impact HDGC has had on their career (1=strongly disagree; 5=strongly agree).

> "It was hard telling someone at first and possible prospect of our future children carrying this gene is something we will need to deal with." – 27-29 y.o. female (participant 5)

Participants overwhelmingly (100%) felt supported by their families in regards to their HDGC diagnosis. The questionnaire asked participants to rate their level of agreement with different statements addressing the impact HDGC has had on six aspects of relationships with family members. Respondents expressed the highest level of agreement to "living with HDGC has helped me know who I can count on in times of trouble" (mean=4.7; Figure 2.4). In describing their relationships, many participants noted the positive impact HDGC has had on their family:

> "Amazing family and friend support. Made me so appreciative of the people I have in my life." — 27-29 y.o. female (participant 5)

> "It has made us stronger and more closer as a unit." — 27-29 y.o. female (participant 6)

Some participants specifically cited the support and understanding of family members who also have HDGC:

> "It helps having family members who have successfully went through surgery and who now for the most part lead relatively normal lives. They keep me positive." — 24-26 y.o. female (participant 14)

Despite the positive aspects of familial relationships, 44% of participants felt HDGC had caused tension and strained relationships in the family. This tension was often related to difficulties in communication and differences in risk perception:

> "Me and my mother have formed a stronger bond, but I feel relationships are a bit strained in my dad's side of the family where the *CDH1* mutation is. It's like an elephant in the room that some people don't want to discuss or face." — 27-29 y.o. female (participant 18)

> "My family is very supportive of my diagnosis except one sister in law who believes genetics have nothing to do with cancer and it's our thoughts that give us cancer, so my gastrectomy was pointless." — 27-29 y.o. female (participant 17)

> "Some family members disapprove of my medical choices, while others stand by me." — 21-23 y.o. female (participant 16) left

The questionnaire also asked participants to rate their level of agreement with different statements addressing the impact HDGC has had on six aspects of their friendships. Participants expressed the highest level of agreement with, "I feel supported by my friends in regard to HDGC" and "living with HDGC has helped me know who I can count on in times of trouble" (mean=4.2; Figure 2.5). In general, participants felt that their friends are supportive, but do not fully understand HDGC:

> "It has created distance with some friends who don't know what to say or do, while strengthening the bond with some of my closest friends." — 27-29 y.o. male (participant 4)

> "My friends have been supportive however it is something that can be rather hard to comprehend. So I feel more support from my family opposed to friends." — 24-26 y.o. female (participant 14)

> "All my friends know for the most part, they're overall really supportive. Some of them don't, I don't think fully understand, and not in a malicious way, but… they're kinda like, 'oh, you're so skinny, you're so lucky.' And it's like, okay, well no." — (participant 8, phone interview)

> "I think it's really difficult for people to understand what this is because it's not saying I have cancer. It's saying I could. And people aren't used to absorbing that kind of information. So the fact that it's not really a straight forward diagnosis… the level of sympathy is not always there." — (participant 26, phone interview)

Half of respondents (50%) agreed with the statement "living with HDGC has caused me to miss out on social activities." Respondents described their struggles with eating and drinking out with friends after PTG:

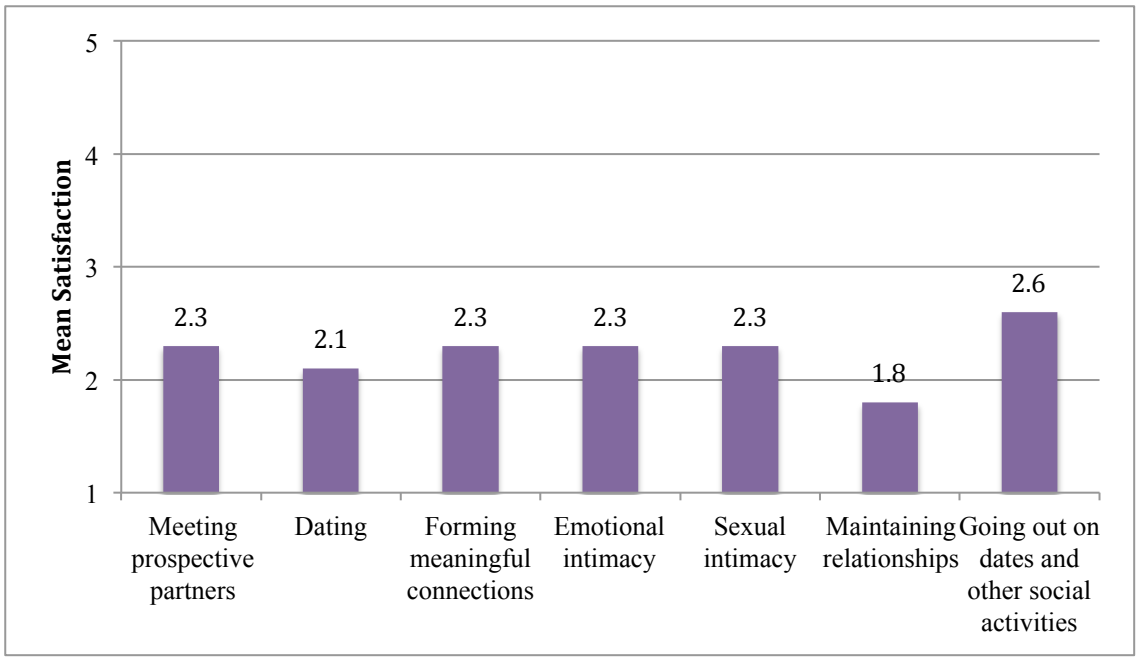

Figure 2.3 Impact on romantic relationships**.** Participants' perceptions of the level of impact HDGC has had on their relationships with romantic partners (1=strongly disagree; 5=strongly agree).

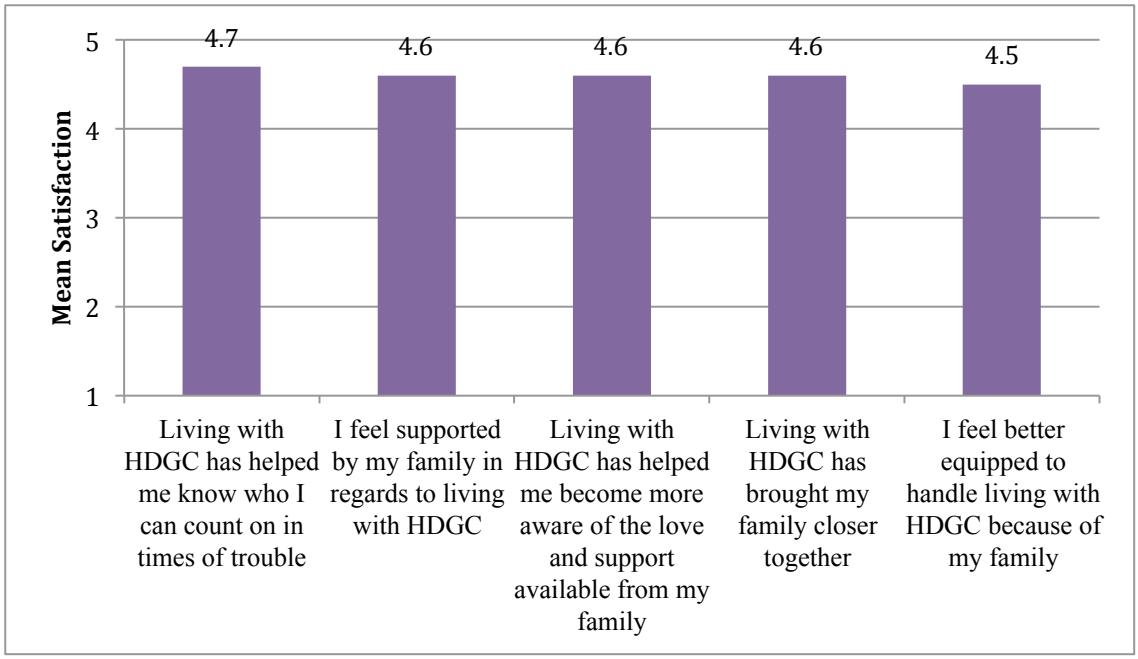

Figure 2.4 Impact on familial relationships**.** Participants' perceptions of the level of impact HDGC has had on their relationships with family members (1=strongly disagree; 5=strongly agree).

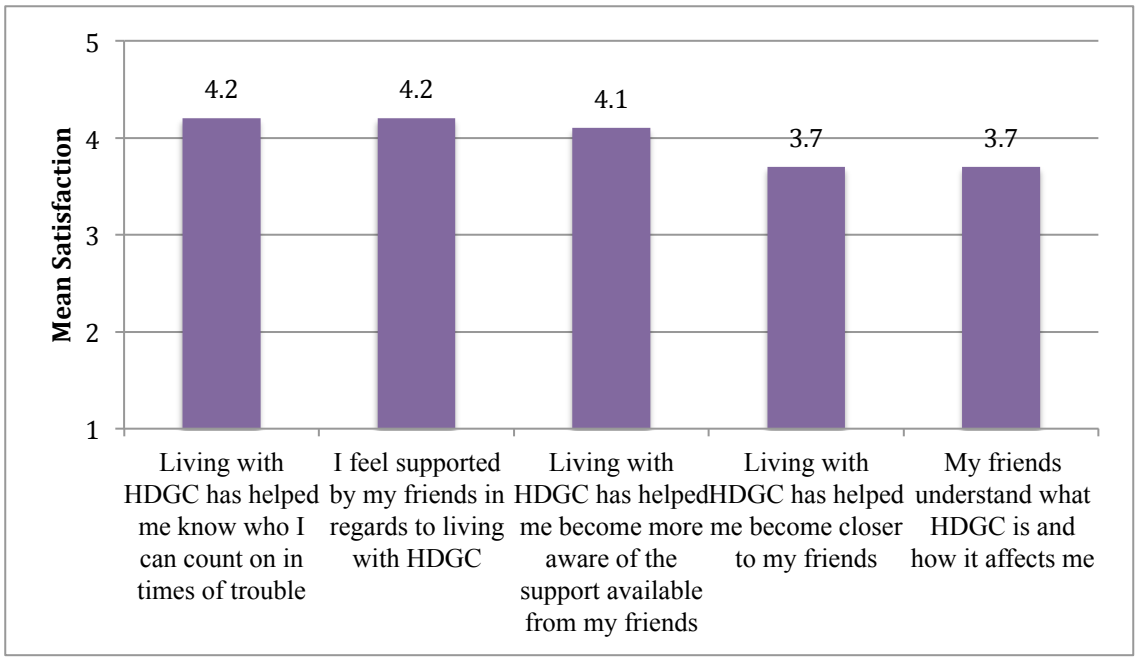

Figure 2.5 Impact on friendships. Participants' perceptions of the level of impact HDGC has had on their friendships (1=strongly disagree; 5=strongly agree).

> "There's been times where I've had to leave a social event early because I've been feeling ill, and especially now for going out for meals with people. I don't feel very comfortable doing that right now." — (participant 18, phone interview)

> "Exhausted, 'grumble guts', and never sure of how much energy I would have tomorrow made me a no show more often than not to most activities including family gatherings and friends nights out." — 27-29 y.o. male (participant 4)

Family Planning

The majority of respondents (83.3%) did not have children. For the three individuals that have children, one had children prior to being diagnosed with HDGC and all individuals had their children naturally without using assisted reproductive techniques. In planning for the future, one individual plans to have more children, and two are undecided. For the respondents without children, 66.7% (n=10) plan to have children in the future, 26.7% (n=4) are undecided, and 6.7% (n=1) do not plan on having children. Of those who plan to have children in the future, 63.6% have considered having children

naturally, 54.6% have considered pursuing IVF and PGD, 27.3% have considered adoption, and 9.09% have considered using a donor egg or sperm (Figure 2.6). When asked to what extent HDGC has influenced the participants' position on having or not having children, the majority of participants (55.1%) chose "a moderate amount" or above (weighted average 3.1). Several participants expressed their desire to have children naturally, without technological intervention:

> "It changes nothing. I will never 'pick' a child out of my eggs. If my parents had that 'option' and if they knew...I wouldn't be here. I will have a kid and we will live this life." — 27-29 y.o. female (participant 6)

> "IVF was not for me. I trusted I would get the children that were meant for me naturally." — 27-29 y.o. female (participant 17)

> "When I first got my diagnosis I felt terrible that I could have possibly passed this on to my daughter. And I really questioned having more children… But after talking with my fiancé and family and doctors, they have all encouraged me to pursue in whichever direction I want. That I shouldn't let my diagnosis determine everything in my life." — 27-29 y.o. female (participant 20)

In contrast, other respondents expressed discomfort and fear at the possibility of their children inheriting the mutation, while expressing varying levels of comfort with the idea using IVF and PGD:

> "I feel almost irresponsible if I have children biologically mine because I don't feel comfortable with PGD. It's a big gamble, and I'm not sure how I feel yet." — 21-23 y.o. female (participant 16)

> "It has affected me so much, I don't want the possibility of me passing this genetic mutation on to my babies." — 18-20 y.o. female (participant 24)

> "The reality of CDH1 means that there is no way I will have biological children - I can't risk passing it on… the chance of me dying young is too high… I can't have kids knowing how likely it is that they would have to go through that." — 27-29 y.o. non-binary (participant 27)

> "I think it's a lot more to sign up for. I think if I were to have children, and I'm currently undecided, it would be through IVF. So it's a big decision in a sense. I won't pursue having children naturally." — (participant 26, phone interview)

Several participants' concerns were largely due to the potential complications of pregnancy after surgery:

> "I wouldn't not have children in fear of the mutation I just worry about the complications that may arise with having a child after surgery." — 24-26 y.o. female (participant 14)

> "Has not influenced my family planning except when will be the right time to do the full gastrectomy." — 21-23 y.o. female (participant 11)

Participants also expressed hope and expectation in advancements in medical technology and cancer prevention techniques:

> "I see it as if my child has this gene, then with how far the medical world has come in 20 years, by the time by child is 18 we could be even more advanced than what we are now..." — 27-29 y.o. female (participant 5)

> "The next few years will tell us a lot about genetics and its impact on us as a species going forward. Crisper could make this discussion null and void inside of a few decades." — 27-29 y.o. male (participant 4)

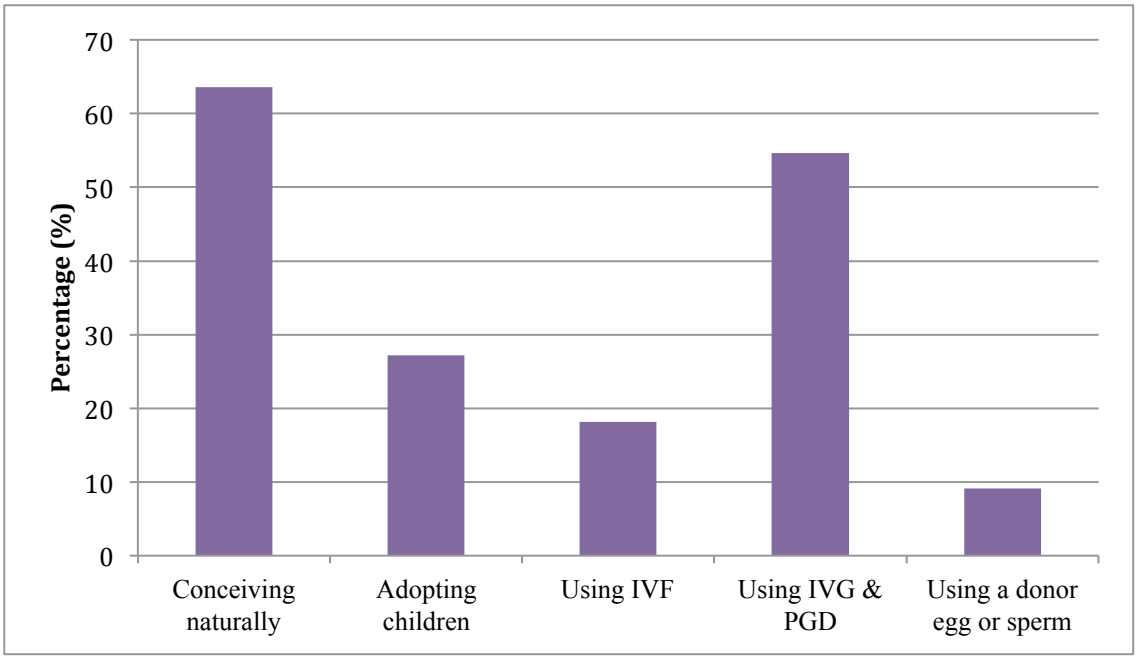

Figure 2.6 Methods of reproductive planning considered by respondents.

Genetic Counseling

Almost all respondents (95%) were seen by a genetic counselor regarding their diagnosis of HDGC. Many respondents (78%) found their genetic counselor to be very useful or extremely useful and agreed (89%) that the genetic counselor had provided them with the appropriate amount of information. Two participants noted negative aspects of their genetic counseling experience in the open-text entry: one felt the genetic counselor had not provided them with information they did not already know from family members, and one was upset with the manner in which they received their results (i.e. voicemail). However, most responses were positive and noted the support and information provided by the genetic counselor:

> "We met with the genetic counselor while also with the surgeon who would later perform my mother's gastrectomy. The surgeon asked me some question about children, and I said something along the lines of 'well, I'm obviously not having kids now.' He acted like what I had said was bizarre or unexpected. The genetic counselor, however, didn't seem surprised and clearly understood where I was coming from. That has stuck with me." — 27-29 y.o. non-binary (participant 27)

> "She told me a lot of information that I didn't already know. I think I only had 1 session with her but she did give a lot of info and was useful." — 27-29 y.o. female (participant 5)

Overall quality of life

Four additional themes emerged from participants' responses during the semi-structured phone interviews and open-text entry questions: (i) the burden of being the expert on HDGC, (ii) the significant impact on mental health, (iii) the use of online communities as a source of support, (iv) and a positive outlook on overall quality of life.

Due to the rarity of HDGC, participants felt frustrated explaining their condition to friends and family members:

> “When you tell them, "my mom doesn't have a stomach," it's kind of a shock. So it's like, people think you can't live without it or something. It's just something that's really hard to explain. So I don't even really go into big detail about it.” — (participant 14, phone interview)

> “I wish there was a like a pamphlet, like an easy, digestible pamphlet, to give to family and friends. It's been years and there's no easy or short way to explain it. And it takes a lot of discussion to understand.” — (participant 26, phone interview)

Participants also expressed frustration with the burden of educating their own healthcare providers on the condition, and sometimes feeling misunderstood:

> “Even at the dentist they ask you to explain your last hospital procedure. So I'm sitting there for 5 to 10 minutes explaining to a dental hygienist what I have wrong with me. It never gets easier.” — (participant 26, phone interview)

> “Being someone in the medical profession as well, it just surprises me sometimes how much a lack of compassion some providers can still have and they are just like, ‘what? a total gastrectomy? what?’” — (participant 8, phone interview)

> “[Describing a nurse] Right after I woke up from my endoscopy, she said ‘so you're going to get the gastrectomy, you've already decided?’ I said ‘yeah, I'm going to get it.’ She was like, ‘but you're so young, have you thought about this, have you thought about this?’ And I was super irritated because she knew nothing… it made me so nervous. I had just woken up from the procedure.” — (participant 9, phone interview)

Several participants struggled with their mental health at various stages in their journey through diagnosis and after PTG. One participant described an onset of anxiety attacks after finding out about her carrier status and ended up seeking help through therapy and medication. Others described serious mental health struggles throughout surgery recovery, both as a result of burdensome physical symptoms, as well as the perceived effect of removing the stomach on brain chemistry:

> “I think the psychological impact is not discussed. Finding out about the mutation was difficult enough, but life post gastrectomy is mentally challenging. I'm aware serotonin is released in the gut and the whole system has changed, which disrupts

this. I think there should be more support offered afterwards." — 27-29 y.o. female (participant 18)

"Emotional health during this procedure was hell. Your brain chemistry is so messed up when you remove your gut and ability to process food they way your body has known. New normal is different and good but takes months to achieve." — 27-29 y.o. male (participant 4)

"Anxiety attacks, medication, seeing a therapist… I feel like I'm sinking half the time but I mean at the end of the day, I mean I'm so lucky to be able to get this surgery and to have a healthy long life after that… but I can't really control the way I feel now." — (participant 9, phone interview)

While struggling with the rarity of the condition and lack of awareness in the general public, participants found comfort and support in online communities for HDGC. They also used these communities as a major source of knowledge regarding cancer risks and surgery:

"It was crucial that I learn about it, especially for where I live. I've literally never met anyone in person that has what I have. It's only been online. Yeah it's been valuable but it's also very much normalized this whole thing." — (participant 26, phone interview)

"I researched a lot [before surgery] and I'm in a few groups online. That helps me with things with like nutrition and vitamins and all these things I didn't necessarily know about that are important." — (participant 18, phone interview)

In response to a question about the impact of having a *CDH1* mutation on overall quality of life, the majority of respondents (56.3%) had a positive outlook. Respondents felt empowered by the knowledge of this mutation and the option to reduce their cancer risk:

"Before my gastrectomy I was riddled with anxiety knowing I had that ticking time bomb inside of me. I spent every family event in my head thinking I need to make it perfect in case this is my last whatever holiday we were celebrating. It was awful. Now I have more peace while celebrating these, and just have to watch everyone eat their good foods and treats I can no longer tolerate." — 27-29 y.o. female (participant 17)

> "My life has changed forever but I have no regrets. I've seen what stomach cancer does and how quickly it takes away a person. I need time to adjust to a new normal. I feel hopeful that I'll get there!" — 27-29 y.o. female (participant 18)

Participants also felt hopeful for the future:

> "I think it has opened my eyes to living in the moment and being grateful for what's around me and the people I have. It affected me negatively just in the beginning. But now I am optimistic for what the future holds." — 27-29 y.o. female (participant 20)

> "It has made it better. I am more aware of everything. Yes I have the down days but man those days make me feel so blessed to be alive. Now don't get me wrong. Not having a stomach can suck. Cancer sucks… but my quality of life is beautiful. And even on the hard days it still is." — 27-29 y.o. female (participant 6)

In contrast, several respondents (18.8%) cited the negative impact their *CDH1* mutation has had on overall quality of life:

> "Yes— it is emotionally and physically very draining." — 24-26 y.o. female (participant 8)

> "Yes 100%, my eating, exercise, sleep, etc!" — 18-20 y.o. female (participant 24)

Throughout open-text entry questions and semi-structured phone interviews, participants demonstrated a strong sense of positivity and resiliency. When asked what advice they would give to someone recently diagnosed with HDGC, many participants emphasized how fortunate they feel to have this information and that this diagnosis doesn't define their life:

> "My token phrase is that everybody's dealt a certain hand of cards and it's how you play them. I think you can look at this as a negative, especially for someone that had no idea this was coming. But I'm really lucky that I [found out about the mutation] because I wouldn't have been here in 5, 10, 20 years… it's not always that bad. I'm lucky to know this is here and taking the steps and taking control of my own health." — participant 26, phone interview

> "…it's not as scary as it initially sounds and it doesn't affect your life in a horribly dramatic way. You just eat smaller amounts of food and you continue on. It's

> basically it's not as life-altering and as scary as you first think when you hear an organ is going to be removed entirely." — participant 20, phone interview
>
> "I simply want people to know that there is life after a total gastrectomy. Because you know, when I when I initially found out about all of this, I had no idea that people could even live without a stomach. I thought that was crazy. It's possible and it's not as hard as it seems." — participant 18, phone interview

2.5 Discussion

This study explored the perspectives of emerging adults (ages 18-29) with a *CDH1* mutation to gain a better understanding of how they are impacted by their carrier status in multiple domains of life: education, career, relationships, and family planning. In addition, we assessed experiences and satisfaction with genetic counseling, as well as perceived overall impact on quality of life. Specific challenges highlighted are missed time at work, strained familial relationships, difficult reproductive decision-making, mental health struggles, and the burden of being the expert on HDGC. Despite these challenges, many participants felt empowered by knowing their mutation status and had a positive outlook on life. They found support in their partners, family and friends, and online support networks.

Education and Career

The greatest challenge participants faced in terms of their career was prolonged absence due to surgery and recovery. After returning to work, participants struggled with fatigue and other post-PTG side effects, which in turn affected performance and attendance. One participant anticipated not being able to return to work full-time as a nurse due to the physical demands of the job, and another reduced her working hours because her day now revolves around eating. These sentiments support findings by Hallowell et al., which found that individuals who had undergone PTG in their early 20s

struggled with feeling left behind in their career as a result of time lost due to surgery and recovery. Additionally, interviewees of all ages cited fatigue as a major issue after surgery that prevented them from returning to work full time (Hallowell et al., 2017b).

Participants were less impacted by HDGC in terms of their education, as evidenced by the lower level of impact across all six categories. One contributing factor to this result may have been the significant number of respondents who finished their education prior to finding out their *CDH1* mutation status. In addition, two participants with impending surgeries noted that while HDGC had not yet impacted their education, they anticipated taking time off for recovery in the future. Of note, several participants found their mutation status to be motivation for their education, as opposed to a hindrance. This is demonstrated by the multiple respondents who cited their experience with HDGC as inspiration for their ambitions in medicine and science.

Relationships with family, friends, and romantic partners

As a whole, relationships with family, friends, and romantic partners were supportive and helpful to respondents. Participants felt most supported by their family members, especially those with HDGC, as they were able to share unique experiences and information with one another. Previous research has found that the experience of having close relatives with cancer can serve as a catalyst for positive changes in behavior, such as revising life priorities and maintaining closer relationships with family in general (McPhail et al., 2016). The participants in this study demonstrate a similar phenomenon, as all participants indicated a known family member with an HDGC-related cancer. In addition, a study by Kenen et al. described participants who felt comforted to share a

BRCA1/2 mutation with family members because it became something they could then cope with as a unit (Kenan et al., 2006).

Despite feeling supported by family in general, participants also felt at odds with some family members regarding their healthcare decisions. Nearly half of respondents (44%) felt HDGC had caused tension and strained relationships in the family, often times due to difficulties in communication and differences in risk perception. These results were similar to the findings of Douglas et al., whose participants with a *BRCA1/2* mutation felt more or less connected to certain family members depending on family cancer history, communication patterns, and mutation status. While sharing a mutation with relatives often created a special bond, there was also tension when family members perceived their cancer risk differently or made contrasting decisions regarding surveillance measures (Douglas et al., 2009). These results further demonstrate that a diagnosis of a cancer-predisposition syndrome involves the family rather than the patient alone.

Regarding friendships, participants largely felt supported by their friends while simultaneously struggling with their lack of understanding about the condition. Going through this experience created distance in some friendships, which participants perceived as their friends not knowing what to say rather than not caring. Participants who had undergone PTG also cited difficulty making plans with friends, especially involving eating or drinking. This sentiment was mirrored in romantic relationships, in which the highest level of impact ranked by participants was "going out on dates and other social activities." Furthermore, single participants experienced anxiety about being with someone new post-PTG and anticipated difficulty in relaying their recurrence risk to

a future partner. These results support findings by Mireskandari et al., which found that young adults with FAP avoided intimate relationships as a result of low self-esteem from surgery scars and changing body image post-surgery. In addition, single young adults with FAP felt apprehensive about discussing the possibility of passing FAP on to future children (Mireskandari et al., 2009).

Family planning

Reproductive decision-making in the context of cancer risk is complex, and participants demonstrated mixed feelings regarding future family planning. When asked which methods of conception they had considered for the future, the highest percentage of participants considered conceiving naturally, followed closely by pursuing IVF with PGD. While many participants felt a responsibility to avoid passing on a *CDH1* mutation to their children, a minority were interested in pursuing options to have non-biological children via adoption or egg/sperm donation. Participants expressed varying levels of comfort with the use of reproductive technology. Several participants were adamantly against PGD and felt that screening embryos invalidated the value of their own existence as a person with HDGC. Others would not consider having biological children at all without ensuring they would not have the mutation. Ormondroyd et al. found a comparable range of opinions when interviewing women diagnosed with a *BRCA1/2* mutation prior to having children. Several interviewees expressed uneasiness with the thought that perhaps they would not exist if their parents had the same reproductive screening options, while others believed they had a moral responsibility to ensure the mutation was not passed down to the next generation (Ormondroyd et al., 2012).

A common theme among many participants considering natural conception was the hope or expectation that future developments in medical technology will render this discussion null and void for their children. Previous research has highlighted a similar sentiment reported by young, female *BRCA1/2* carriers, some of who held strong beliefs that new treatments and preventive measures will be more successful for their children (Donnelly et al., 2013). In addition, female participants struggled with the logistics of balancing the need for risk-reducing surgery (gastrectomy and/or mastectomy) and the timing of pregnancy. Several of these themes were reflected in a 2017 study by Hallowell et al., in which interviewees expressed a spectrum of opinions on reproductive options for *CDH1* carriers. While the majority of childless interviewees were unsure of whether to pursue reproductive testing, many were open to the idea of utilizing IVF with PGD to screen embryos (Hallowell et al., 2017a). These results reflect the diversity of views held by emerging adults when considering family planning and highlight the critical need for reproductive counseling.

Genetic Counseling

Genetic counselors are trained to provide education on the genetic basis of disease and recurrence risk, in addition to assessing the psychosocial needs of each patient (Schneider, 2012). Almost all participants in this study were seen by a genetic counselor when being tested for a *CDH1* mutation. The majority of participants felt their genetic counseling session was useful and that they were provided with the appropriate amount of information. Several participants also mentioned feeling compassion and understanding from genetic counselors specifically, sometimes in contrast to other healthcare providers. These results suggest that in the context of counseling for HDGC,

genetic counselors should continue to approach patients with compassion and empathy, in addition to providing resources to support organizations. Genetic counselors should also be mindful to ask patients how they would like to receive their results and accommodate patients accordingly (Schneider, 2012).

Living with a rare condition

Due to the rarity of HDGC, participants often felt frustrated with the responsibility of explaining this condition to others. They found people were unfamiliar with the concept of cancer predisposition in general and skeptical about the possibility of living without a stomach. As a result, they often respond with incredulity rather than sympathy. Participants desired an accessible resource such as a pamphlet or booklet that they could give out rather than attempting to explain the condition themselves. Respondents were especially burdened by a lack of knowledge among their own healthcare providers and utilized online communities for medical information and surgeon recommendations. Additionally, online networks such as No Stomach For Cancer and Facebook support groups helped lessen the feeling of isolation among respondents, connecting them over long distances and providing a sense of community. Similarly, Ross et al. found that online blogs functioned as a means to connect individuals in the FAP community. Much like the responses from emerging adults with HDGC, FAP bloggers noted the poor understanding of their condition amongst medical professionals and within their social circles. Bloggers utilized their online space to share their own experiences and provide advice to others with the condition (Ross et al., 2018).

Mental health & overall well-being

Several participants struggled with their mental health at various stages in their journey through diagnosis and after PTG. Prior research studies have demonstrated that approximately 40% of emerging adults in the USA meet criteria for a psychiatric disorder, most commonly anxiety or substance abuse (Arnett et al., 2014). Given this background risk, emerging adults dealing with the added stress of cancer risk and major surgery may have an increased risk of developing a mental illness. Several participants described serious mental health struggles throughout surgery recovery, both as a result of burdensome physical symptoms, as well as the perceived effect of removing the stomach on brain chemistry. These responses highlight the need to discuss the psychosocial implications of surgical recovery earlier in the decision-making process, in addition to following up with patients long-term after surgery.

Despite the psychological impact of HDGC, respondents had an overwhelmingly positive response when asked how this condition had impacted their overall well-being. Many expressed how thankful they are to have found out about their carrier status at all. They find it empowering to be able to take steps to reduce their cancer risk, either by surveillance or undergoing surgery. Previous research on the psychosocial impact of undergoing PTG has found relief of anxiety regarding gastric cancer risk to be a major benefit of undergoing surgery (Hallowell et al., 2017b). This sentiment mirrors the participants of this study, many of whom perceived the option of risk-reducing surgery to be a positive step in managing cancer risk. In addition, participants noted the unique perspective they have gained from having a family history of cancer and facing their own cancer risk. A theme of positive personal outcomes has previously been reported in

individuals with a family history of cancer, in which interviewees discussed having greater maturity and compassion, as well as maintaining a perspective on the important things in life (McPhail et al., 2017). Similarly, participants in this study were well adjusted to their diagnosis and had a positive outlook for the future.

Practice Implications

It is critical that healthcare providers take a holistic approach in the care for emerging adults with a *CDH1* mutation. Given the results of this study, providers should recognize the unique challenges that come from a diagnosis of HDGC in the context of the individual's stage of life. Below are practice recommendations for genetic counselors and other providers caring for the HDGC population based on the results of this study:

1. **Genetic counselors should consider the needs of the emerging adult demographic as they provide anticipatory guidance for managing all aspects of the condition.** This guidance includes recognizing the potential impact on education, career, and relationship-dynamics.
2. **Genetic counselors should be prepared to present all reproductive options to individuals with HDGC.** This not only includes counseling on recurrence risk and assisted reproduction therapies but also includes being able to address childbearing pre- vs. post-gastrectomy. Structured follow-up or referrals may be helpful to readdress family planning as individuals and couples consider these decisions over time. In addition, information regarding pregnancy after PTG is available through No Stomach For Cancer.
3. **Genetic counselors and other providers should be aware of and continue to develop resources for individuals with HDGC.** As healthcare providers

specially trained to communicate complex genetic concepts, genetic counselors are in a unique position to find or create the educational materials desired by patients with HDGC to give to family, friends, and healthcare providers. Emerging adults should also be made aware of networks such as No Stomach For Cancer, which many participants cited as a significant source of support and information.

4. **Genetic counselors should recognize and address the significant psychological impact of this diagnosis and encourage referrals to mental health services.** This is needed especially for emerging adults given the background risk of a psychiatric disorder.

Limitations and Future Research

The results of this study are limited by a small sample size (n=21), which inhibited accurate comparisons between groups (e.g. pre- or post-PTG, single vs. married). In addition, our demographics were heavily skewed towards female and Caucasian participants and cannot be generalized to ethnic minority or male *CDH1* carriers. Lastly, participants were recruited through international support networks and the results are limited to the reflections of individuals connected to the support groups through Facebook. It is possible this sample represents *CDH1* carriers that are exceptionally motivated to act or to seek help, with increased access to educational materials through the connections to online communities. Differing opinions and additional themes may arise from emerging adults with HDGC who are not connected to online support groups. We believe that a similar study with a larger sample size may yield a more diverse participant population and statistically significant results when

comparing between groups. Alternate methods of recruitment, such as through a medical system as opposed to support groups, could also give rise to different viewpoints. Furthermore, it is possible the perspectives captured in this study are representative of a broader age range of individuals with HDGC, rather than emerging adults only. Additional research is needed to assess the impact of HDGC in individuals of all ages.

CHAPTER 3

CONCLUSIONS

This study explored the perspectives of emerging adults with a *CDH1* mutation to gain a better understanding of how they are impacted by their carrier status in multiple domains of life: education, career, relationships, and family planning. We also assessed experiences and satisfaction with genetic counseling and overall quality of life. Specific challenges highlighted were missed time at work, strained familial relationships, difficult reproductive decision-making, mental health struggles, and the burden of being the expert on HDGC. Despite these challenges, many participants felt empowered by knowing their mutation status and had a positive outlook on life. They found support in their partners, family and friends, and online support networks. The results of this study provide a glimpse into the lived experience of emerging adults with hereditary diffuse gastric cancer and distinguish the unique needs of these individuals after diagnosis. While HDGC is rare, genetic counselors will increasingly interact with patients receiving positive results for a *CDH1* mutation as the utilization of multi-gene panels for oncology testing continues to increase. Overall, a need exists to raise awareness of HDGC and have educational materials in place so this information is conveyed effectively to healthcare providers. In addition, it is critical that healthcare providers take a holistic approach in the care for emerging adults with a *CDH1* mutation. While providing the appropriate medical treatment and guidance, providers should be sensitive to patients' informational and psychosocial needs in the midst of rapid social and professional development.

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APPENDIX A

DEMOGRAPHIC TABLE

Characteristics	**Response**	***n***	**(%)**
Gender	Male	4	19.0
	Female	16	76.2
	Non-binary	1	4.8
Age (years)	18-20	2	9.5
	21-23	4	19.0
	24-26	5	23.8
	27-29	10	47.6
Ethnicity	White or Caucasian	20	95.2
	Hispanic/Latino	1	4.8
Highest level of education	Completed high school	4	19.0
	Some college	5	23.8
	Trade/technical/vocational training	2	9.5
	Bachelor's degree	6	28.6
	Master's degree	2	9.5
Region of residency	United States	13	61.9
	International	8	38.1

APPENDIX B

ONLINE QUESTIONNAIRE

Hello,

Thank you for participating in my graduate research study. The goal of this study is to gather information about what life is like for individuals aged 18-29 with a *CDH1* mutation. We are curious about multiple areas of your life including education, employment, and planning a family. We would also like to know how Hereditary Diffuse Gastric Cancer (HDGC) has impacted your relationships with family, friends, and partners. Your answers will help genetic counselors, doctors, and other healthcare providers better support and care for patients who have HDGC.

Important things to know about this study:

- The survey is open to anyone currently aged 18 to 29 who has a *CDH1* mutation. We also ask that you encourage eligible family members and/or friends to take the survey.
- The survey will take approximately 20 minutes to complete.
- The survey is anonymous and participation is voluntary.
- You can skip any question(s) you are not comfortable answering and may exit the survey at any time.
- The survey will be available until January 31, 2019.

This study was reviewed and approved by the University of South Carolina Institutional Review Board. If you have any questions about this research project, please contact Carrie Anderson at carrie.anderson@uscmed.sc.edu, or the University of South Carolina faculty advisor, Emily Jordon, at emily.jordon@uscmed.sc.edu

Thank you again for your time and participation!

Sincerely,

Carrie Anderson
MS candidate in Genetic Counseling
University of South Carolina, School of Medicine

Hereditary diffuse gastric cancer (HDGC) is an inherited cancer syndrome that increases the chances of developing both diffuse gastric cancer and lobular breast cancer. "Hereditary diffuse gastric cancer" is the name of the syndrome. People who inherit the *CDH1* mutation are considered to have HDGC, even if they themselves have not developed cancer.

1. By clicking "Yes," you consent to participate in our study.
    a. Yes
    b. No [if no is selected, skip to end of survey]
2. Are you currently between the ages of 18-29 years?
    a. Yes
    b. No [if no is selected, skip to end of survey]
3. How old are you?
    a. 18-20
    b. 21-23
    c. 24-26
    d. 27-29
4. Which of the following best represents your race/ethnicity?
    a. American Indian/Native American
    b. Asian
    c. Black/African American
    d. Hispanic/Latino
    e. Native Hawaiian/Pacific Islander
    f. Non-Hispanic White
    g. Other (please specify): _____
5. Which of the following do you identify as?
    a. Female
    b. Male
    c. Prefer to self-describe: _____
6. In which country do you live?
        a. USA
        b. Other (please specify) _____
7. [If "USA" to Q6] In which state do you live: _____
8. Have you had genetic testing for HDGC?
    a. Yes
    b. No [skip to end of survey]

9. [If "yes" to Q8] What was the result of that test?
    a. Positive (you have an identified *CDH1* gene mutation)
    b. Negative (you do not have a *CDH1* gene mutation) [skip to end of survey]
    c. Uncertain result (variant of uncertain significance, VUS) [skip to end of survey]

The following set of questions will ask you about your own medical history and your family history in relation to Hereditary Diffuse Gastric Cancer (HDGC).

10. How old were you when you had genetic testing for a *CDH1* mutation? ___
11. Have any of your relatives also tested positive for a *CDH1* mutation? Please select all that apply
    a. I am the only person in my family who has tested positive for a *CDH1* mutation
    b. Yes, my mother/father has a *CDH1* mutation
    c. Yes, my sibling(s) has/have a *CDH1* mutation
    d. Another relative has a *CDH1* mutation. Please list all other relatives with HDGC (for example: cousin, aunt, etc): _____
12. Have you ever been found to have stage 1 stomach cancer cells (signet ring cells) on screening?
    a. Yes
    b. No
    c. I have not had any screening
    d. I don't know
13. [If "yes" to Q12] How old were you when you were first found to have stage 1 stomach cancer cells _____
14. Have you had your stomach surgically removed?
    a. Yes
    b. No
15. [If "yes" to Q14] How old were you when you had your stomach removed? _____
16. Have you ever been diagnosed with cancer?
    a. Yes
    b. No
    c. I don't know
17. [If "yes" to Q16] With which type of cancer were you diagnosed? Please choose all that apply.

a) Stomach
b) Breast
c) Colon
d) Other (please specify): _____

18. [If "yes" to Q17a] How old were you when you were first diagnosed with stomach cancer? _____
19. Have any of your family members or relatives with a *CDH1* mutation ever been diagnosed with cancer?
    a. Yes
    b. No
    c. I don't know
20. [If "yes" to Q18] Please specify which of your relatives with a *CDH1* mutation have been diagnosed with cancer and with what type.

	Stomach cancer	Breast cancer	Colon cancer
Mom / Dad			
Brother(s)			
Sister(s)			
Grandparent(s)			
Aunt(s) / Uncle(s)			
Cousin(s)			

21. [If "yes" to Q17] Have any of these family members or relatives passed away due to cancer caused by HDGC? (Please list relatives).

The following questions will ask you to think about how your diagnosis of HDGC has or has not impacted your education.

22. What was the highest degree or level of education you have completed?
    a. Some high school

b. Completed high school
c. Some college
d. Trade / Technical / Vocational training
e. Associate degree
f. Bachelor's degree
g. Master's degree
h. Doctorate degree

23. How do you feel about the following statements:

a. Having HDGC has…

	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree
Had a negative impact on my education					
Had a positive impact on my education					
Limited my ability to move away for school					
Affected my class attendance					
Impacted my performance in school					
Impacted what I chose to study					
Impacted the timing in which I pursued my education					

24. Please use the space below to elaborate on any of the above statements and/or tell us more about how your diagnosis of HDGC has or has not impacted your education:

The following questions will ask you to think about how your diagnosis of HDGC has or has not impacted your career choices and work life.

25. Which option best describes your current employment status?
    a. I am currently working in the field I would consider my career
    b. I am currently working, but in a field I would consider temporary
    c. I am not currently working due to reasons involving HDGC (e.g. recovering from gastrectomy)
    d. I am not currently working for other reasons (e.g. school, personal choice)
    e. I have never been employed [skip to next section]
26. How do you feel about the following statements:
    a. Having HDGC has…

	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree
Had a negative impact on my career					
Had a positive impact on my career					
Influenced my choice of career					
Affected my performance at my job					
Limited my ability to move away for a job					
Caused me to have to take time off work					
Kept me from advancing to a higher position					

27. Please use the space below to elaborate on any of the above statements and/or tell us more about how your diagnosis of HDGC has or has not impacted your career:

The following questions will ask you to think about how your diagnosis of HDGC has or has not impacted your relationships with romantic partners, family members, and friends.

28. What is your current relationship status?
    a. Single
    b. In a committed relationship
    c. Married
    d. Domestic Partner
    e. Separated
    f. Divorced
    g. Widow/Widower
29. How much would you say your diagnosis of HDGC has impacted the following aspects of your romantic relationships?

	None at all	A little	A moderate amount	A lot	A great deal
Meeting prospective partners					
Dating					
Forming meaningful connections					
Emotional intimacy					
Sexual intimacy					
Maintaining relationships					
Going out on dates and other social activities					

30. Please use the space below to elaborate on any of the above statements and/or tell us more about how your diagnosis of HDGC has or has not impacted your romantic relationships:
31. Please rate the following statements in terms of how they apply to only your relationships with **family members**.

	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree
Living with HDGC has helped me know who I can count on in times of trouble					
I feel supported by my family in regards to living with HDGC					
Living with HDGC has helped me become more aware of the love and support available from my family					
Living with HDGC has brought our family closer together					
HDGC has caused tension / strained relationships within the family					
I feel better equipped to handle living with HDGC because of my family					

32. Please use the space below to elaborate on any of the above statements or tell us more about how your diagnosis of HDGC has or has not impacted relationships with family members.

33. Please rate the following statements in terms of how they apply to only your relationships with your **friends.**

	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree
Living with HDGC has helped me know who I can count on in times of trouble					
Living with HDGC has helped me become closer to people I care about					
Living with HDGC has helped me become more aware of the support available from my friends					
Living with HDGC has caused me to miss out on social activities					
My friends understand what HDGC is and how it affects me					
I feel supported by my friends in regards to living with HDGC					

34. Please use the space below to elaborate on any of the above statements and/or tell us more about how your diagnosis of HDGC has or has not impacted your relationships with your friends.

The following questions will ask you to think about how your diagnosis of HDGC has or has not impacted your decisions about having children.

In vitro fertilization (IVF) with preimplantation genetic diagnosis (PGD): IVF with PGD is an assisted reproductive technique that allows an embryo to be tested for a *CDH1* mutation before it is implanted into the woman's uterus. Only embryos that do not have the mutation are implanted.

35. Do you have children?
    a. Yes
    b. No
36. (If "yes" to Q35) Did you have your children before you were diagnosed with HDGC?
    a. Yes
    b. No
37. (If "no" to Q36) Please check all that apply
    a. I had my child(ren) without using assisted reproductive techniques (I conceived naturally)
    b. I had my child(ren) using in vitro fertilization (IVF)
    c. I had my child(ren) using in vitro fertilization and pre-implantation genetic diagnosis (IVF and PGD)
    d. I had my child(ren) using a donor egg or donor sperm
    e. My child(ren) is/are adopted
38. (If "yes" to Q35) Do you plan to have more children?
    a. Yes
    b. No
    c. I haven't thought about it yet
    d. I am undecided
39. (If "no" to Q35) Do you plan to have children?
    a. Yes
    b. No
    c. I haven't thought about it yet
    d. I am undecided
40. (If "yes" to: do you plan to have more children? Do you plan to have children?) Which of the following have you considered for having future children, or are undergoing already? Check all that apply
    a. Having children without using assisted reproductive technologies (conceiving naturally)
    b. Adopting children

c. Using in vitro fertilization
d. Using in vitro fertilization and pre-implantation genetic diagnosis
e. Using a donor egg or sperm

41. To what extent has your diagnosis of HDGC influenced your position on having or not having children?
    a. A great deal
    b. A lot
    c. A moderate amount
    d. A little
    e. None at all
42. Please use the space below to tell us more about how your diagnosis of HDGC has or has not influenced your family planning:

The following questions will ask you to think about your experiences with a genetic counselor (if any) and/or other healthcare providers.

43. Have you ever seen a genetic counselor regarding your diagnosis of HDGC?
    a. Yes
    b. No [skip to Q47]
44. [If "yes" to Q43] How would you rate your overall experience with your genetic counselor?
    a. I thought my genetic counseling session(s) was/were…
        i. Not at all useful
        ii. Slightly useful
        iii. Moderately useful
        iv. Very useful
        v. Extremely useful
        vi. I don't remember my genetic counseling session [skip to Q46]
45. To what extent do you agree/disagree with the following statements about your genetic counseling session?

	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree

The genetic counselor provided me with an appropriate amount of information					
The genetic counselor answered all the questions I had in a satisfactory manner					
The genetic counselor was sensitive and attentive to my needs and emotions					
The genetic counselor made me feel supported and comfortable					

46. Please use the space below to elaborate on any of the above statements or tell us anything else about your experience(s) with your genetic counselor and/or other healthcare providers.
47. Do you think having a *CDH1* mutation has affected your overall quality of life? Please use the space below to elaborate.
48. If there is anything else that you would like to share with us about living with HDGC that we have not addressed in this survey, please use the space below:
49. Thank you for completing my survey! We are interviewing a subsection of participants over the phone to gain further insight. If you would like to participate, please provide your contact information below and we may contact you to schedule an interview:
    a. Name
    b. Email address
    c. Phone number

APPENDIX C

TELEPHONE INTERVIEW GUIDE

Informed consent statement:

You are agreeing to participate in a telephone interview as a part of a genetic counseling graduate school research project. This goal of this study is to gain perspective from emerging adults ages 18- 29 about how having hereditary diffuse gastric cancer has affected your life. The findings of this study may provide future benefit to others with HDGC. Your participation in this project is voluntary and you may choose to end the interview at any time. If at any time there is a question you are not comfortable answering, please let me know and we can proceed on to the next question. The interview will last approximately 30 minutes.

With your consent, this conversation will be recorded and transcribed. All responses gathered from the interviews will be kept anonymous and confidential. If a quotation is used from this interview, all identifying information will be removed and you will be assigned an alternative name.

Before we begin, do you have any questions?

1. Can you tell me about the cancers in your family?
    a. What happened? When?
2. What age were you when you first learned about HDGC?
    a. How do you recall finding out about the chance for you to have HDGC?
3. What motivated you to have genetic testing?
4. Have you had or do you plan to have a prophylactic total gastrectomy?
    a. Why or why not?
5. How has having a *CDH1* mutation impacted your education?
6. How has having a *CDH1* mutation impacted your employment?
7. How has having a *CDH1* mutation impacted your social life?
8. How has having a *CDH1* mutation impacted your friendships?
    a. Do your friends have a good understanding of what HDGC is?
    b. Do you feel supported by your friends in regards to HDGC?
9. How has having a *CDH1* mutation impacted your family relationships?
    a. How does your family communicate about HDGC? Is it an open topic?
10. How has having a *CDH1* mutation impacted your romantic relationships?
11. How has having a *CDH1* mutation impacted your plans for having children?
12. How did finding out about your *CDH1* mutation affect your life plans?
13. Is there anything you wish you would have been told upon diagnosis?

14. What do you want medical professionals who are working with HDGC patients to know?
15. What would you like to say to future individuals in your position?