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Low rates of cascade genetic testing among families with hereditary gynecologic cancer: An opportunity to improve cancer prevention☆

Natalie E. Griffin [b], Tommy R. Buchanan [a], Stephanie H. Smith [a], Andrea A. Leon [a], Melissa F. Meyer [b], Jingxia Liu [c], Rachel G. Tabak [d], Katherine C. Fuh [a], Premal H. Thaker [a], Matthew A. Powell [a], David G. Mutch [a], L. Stewart Massad [a], Graham A. Colditz [d, e], Andrea R. Hagemann [a, *]

[a] Division of Gynecologic Oncology, Washington Universiy, St. Louis, MO, USA
[b] Washington University School of Medicine in St Louis, St. Louis, MO, USA
[c] Division of Public Health Sciences, Washington University, St. Louis, MO, USA
[d] Institute for Public Health and Washington University, St. Louis, MO, USA
[e] Department of Surgery, Washington University, St. Louis, MO, USA

HIGHLIGHTS

- *BRCA 1/2* carriers report higher rates of cascade genetic testing in their families compared to those with Lynch Syndrome.
- Less than half of at-risk first-degree family members go on to obtain testing for germline *BRCA* or Lynch mutations.
- Cascade genetic testing rates are significantly higher in female family members compared to male family members.
- Letters to at-risk family members by gynecologic oncology practices may facilitate cascade genetic testing.

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ABSTRACT

Objective: Cascade genetic testing (CGT) of hereditary breast and ovarian cancer (HBOC) or Lynch Syndrome (LS) patients' relatives offers opportunities to prevent cancer, but CGT rates are not well described. We aimed to measure reported disclosure of genetic testing results and CGT rates in these families and evaluate patients' views of educational media.

Methods: Patients with HBOC or LS identified from germline genetic testing at an academic institution between 2011 and 2016 were surveyed regarding disclosure, testing among relatives, and perceptions of educational materials. Medical records and pedigrees provided numbers of total and first-degree relatives.

Results: Of 103 mutation carriers consented, 64 (63%) completed the survey an average of 38 months after receiving genetic testing results. Participants' mean age was 53 years, and thirty-one (48%) had a cancer diagnosis. The majority (86%) felt extremely or very comfortable sharing health information. Participants disclosed results to 87% of first-degree relatives, but reported that only 40% of first-degree relatives underwent testing. First-degree female relatives had significantly higher CGT rates than first-degree male relatives (59% versus 21%, $P < 0.001$). Participants with HBOC reported higher CGT rates than those with LS (49% versus 33%, $P = 0.02$). Participants did not identify any one educational medium as more helpful than the others for disclosing results.

Conclusion: Disclosure rates are high among HBOC and LS mutation carriers, but reported CGT rates are low. Gender- and mutation-specific barriers prevent patients' family members from undergoing CGT. Future studies should implement materials to address these barriers and improve CGT rates.

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* Corresponding author. 660 S. Euclid Ave, Campus Box 8064, St. Louis, MO, 63110, USA.
E-mail addresses: hagemanna@wustl.edu, hagemanna@wudosis.wustl.edu (A.R. Hagemann).

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1. Introduction

Of the 22,000 ovarian cancer and 63,000 endometrial cancer cases diagnosed in the United States in 2018, over 6500 were caused by germline mutations [1–5]. The most common classes of mutations in patients with these cancers are *BRCA1/2* mutations, associated with hereditary breast and ovarian cancer (HBOC), and mismatch repair gene mutations, associated with Lynch syndrome (LS). Together, HBOC and LS mutations cause an estimated 17,000 breast and 14,000 colorectal cancers per year, as well as numerous pancreatic, prostate, and melanoma cancers [4,5]. In the general population, roughly 1 in 300 people have HBOC mutations and 1 in 280 have LS mutations [6]. In contrast, a first-degree relative of a patient with an HBOC or LS mutation has a 50% chance of carrying the same mutation. If identified as a mutation carrier, that person could benefit from early detection and treatment (e.g., regular colon cancer screening and polyp removal) or prevention (e.g., mastectomy, hysterectomy, or salpingo-oophorectomy for breast, endometrial, or ovarian cancer, respectively) [7,8].

Given the potential to prevent cancers, the Society for Gynecologic Oncology, the National Comprehensive Cancer Network, and others recommend genetic screening of all ovarian cancer patients [9], and the Institute of Medicine recommends rapid dissemination of genetic testing to relatives of patients found to have germline cancer mutations [10]. Such cascade genetic testing (CGT) occurs as follows: cancer patients undergo genetic testing, then disclose results to at-risk relatives, who then pursue their own genetic testing. However, in 2017, fewer than 1 in 5 patients with HBOC had undergone genetic testing [11]. Although awareness has increased, CGT rates are even lower. For example, in a study of 115 patients with *BRCA1/2* mutations, 77% of patients informed at least one relative about their genetic testing results, but only half of relatives underwent testing [12]. Other studies report that as few as 9% of at-risk relatives pursued testing [13,14]. Thus, identifying barriers to, and strategies to improve, CGT could improve cancer prevention.

In disclosing germline mutation results and encouraging CGT, patients and relatives face barriers such as financial constraints, lack of knowledge, family discord, and emotional difficulty [12,14–18]. The primary objectives of this study were to describe current disclosure and CGT rates among patients with HBOC or LS who underwent genetic counseling and testing at a single academic center's Division of Gynecologic Oncology. A secondary goal was to assess patients' perceptions of the helpfulness of materials that could be used in the clinic to increase CGT.

2. Methods

2.1. Participants

The Washington University Institutional Review Board approved this survey study. We used a database maintained by our genetic counselor within the Division of Gynecologic Oncology to identify women and men who underwent counseling and tested positive for a germline mutation in one or more genes associated with HBOC or LS between January 2011 and December 2016. Patients included those with cancer or those referred for testing because of high familial risk. Only living participants were included. Patients were recruited, and all surveys were completed, between February 2018 and June 2018. If patients were scheduled for an upcoming appointment, we obtained consent and then offered them surveys in person. Otherwise, we invited patients to participate and obtained consent via telephone, and them emailed them a link to the survey. Only participants who completed the entire survey were included in the analysis. Family pedigrees generated at all genetic counseling visits between 2011 and 2016 were available for reference in the electronic medical record.

2.2. Surveys and disclosure and CGT rate calculations

Survey questions were created with guidance from the Washington University Dissemination & Implementation Research Core. The survey included 25 questions and took approximately 15 min to complete. Participants reported the specific relatives to whom they disclosed their genetic testing results and, if known, the specific relatives who subsequently underwent testing. The patient-reported numbers of relatives to whom information was disclosed were used as the numerators to calculate disclosure rates, and the numbers of family members reported to have undergone testing were used as the numerators to calculate CGT rates. In both calculations, the numbers of relatives at risk for carrying the germline mutation, as determined from the family pedigrees, were used as the denominators. Deceased relatives or those under 18 years old, as recorded on the pedigrees, were excluded from the numbers of at-risk relatives as they would not be available or appropriate for testing. Disclosure and CGT rates were calculated for both the total number of relatives at risk and the number of first-degree relatives at risk. No data were collected directly from relatives.

2.3. Information collected

The following demographic information was collected: patient gender, age, race, education level, annual income, relationship status, cancer history (presence of cancer diagnosis, location, stage, grade, and current disease status), germline mutation status, and treatments. Patients reported the time between when they received their testing results and when they disclosed their results to relatives, their feelings of preparedness to disclose, their comfort in discussing health information with family members, use of resources apart from the genetic counseling visit, and communication strength within the family. Participants were encouraged to report reasons for not disclosing results to relatives, both with selectable options and space for open-ended comments.

Participants were offered educational materials that they had not seen during their initial genetic counseling appointment. These included: (1) a standardized letter to relatives written by the genetic counselor explaining that first-degree relatives have a 50% risk of carrying the mutation and describing the importance of testing, (2) links to four websites with mutation information, (3) a brochure with mutation and testing information, and (4) links to two, 2-min videos explaining the importance of genetic testing for *BRCA 1/2* or LS mutations. Patients reported whether they viewed each of these materials. Regardless of whether or not they viewed the material, they were asked to indicate the extent to which they thought each material would help them understand their own diagnosis or help them disclose risk to family members.

2.4. Statistical analyses

Demographic information for mutation carriers with and without cancer was compared by using the Chi-square or Fisher's Exact tests, as appropriate, for categorical variables and the Kruskal-Wallis test for continuous variables. Paired t-tests were used to compare cascade genetic testing rates between male and female family members. Linear regression models were used to test the relationship between variables of interest and the outcomes of disclosure or CGT rates. The least-square means and 95% confidence intervals were calculated. Patients' ZIP codes were used to compare CGT rates by the distance the patients traveled to the cancer center ($\leq$25 miles, 25–50 miles, and >50 miles). All statistical tests were two-sided using an $\alpha = 0.05$ level of significance. SAS version 9.4 (Cary, NC) was used for all statistical analyses.

3. Results

3.1. Demographics

We identified 195 mutation carriers in the genetic counseling database from 2011 to 2016 and attempted to contact the 154 who were alive and for whom genetic testing records were available in the electronic health record. Researchers approached 25 patients at office visits and attempted to contact the other 129 by telephone. Of the 128 patients reached in person or by phone, 103 consented to participate in the survey. One participant subsequently withdrew, and one died of cancer before completing the survey. Of the remaining 101 participants, 64 completed the survey (63%). Fig. 1 summarizes the flow of the study design, including information known regarding non-participants. On average, participants completed the survey 38 months (range, 15–104 months) after undergoing genetic testing. Table 1 summarizes participant characteristics.

Of the 64 participants completing the survey, 97% were Caucasian. The average age was 53 years (range 24–78 years, median 57 years). Sixty (94%) were female and four (6%) were male. Participants were from unique, non-overlapping families. Thirty-one (48%) had a cancer diagnosis before testing, and 33 (52%) had no history of cancer but sought testing because of high risk or a known germline mutation in a family member. Among the 31 participants with cancer, 15 (48%) had ovarian cancer, 10 (32%) had endometrial cancer, 3 (10%) had colorectal cancer, 2 (6%) had both ovarian and uterine cancer, and 1 (3%) had breast, ovarian, and uterine cancer. One participant's final cancer diagnosis was not found in the electronic medical record. Cancer patients represented all stages, grades, and recurrence status. All participants with cancer received treatment with surgery, chemotherapy, or a combination of surgery, chemotherapy, and/or radiation. Among the 32 participants with no cancer history, 16 (50%) underwent one or more risk-reducing procedures (hysterectomy, bilateral salpingo-oophorectomy, or bilateral mastectomy). Fifty percent of mutations among all 64 participants were HBOC mutations and 48% were LS; one participant (2%) had two clinically significant mutations (*MLH1* and *RAD51D*).

3.2. Disclosure and cascade genetic testing rates

Of the 64 participants, 62 (97%) reported disclosing genetic results to at least one relative. Fifty-two (81%) participants disclosed results to relatives within 6 months of testing, 3 (5%) disclosed results between 6 and 12 months, 2 (3%) disclosed results between 1 and 2 years, and 3 (5%) disclosed results after more than 2 years. Four participants did not answer this question. Fig. 2 depicts participant-reported disclosure and CGT rates. Together, the 64 participants had a total of 1955 family members identified from pedigree review, and they reported disclosing results to 312 (87% ± 33%) first-degree family members and 745 (38% ± 27%) of all at-risk family members. Participants reported that, after disclosing their results, an average of 40% (±29%) of at-risk first-degree family members and 30% (±10%) of all at-risk family members underwent genetic testing. Participants reported that first-degree female family members were significantly more likely to undergo CGT than male family members. On a per family basis, the mean CGT rate was 59% for first-degree females vs. 21% for first-degree males, $P < 0.001$. Similarly, among all at-risk family members, females had a significantly higher CGT rate compared to males (51% vs. 21%, $P < 0.001$). The rates of disclosure and CGT did not differ between participants with and without cancer (not shown).

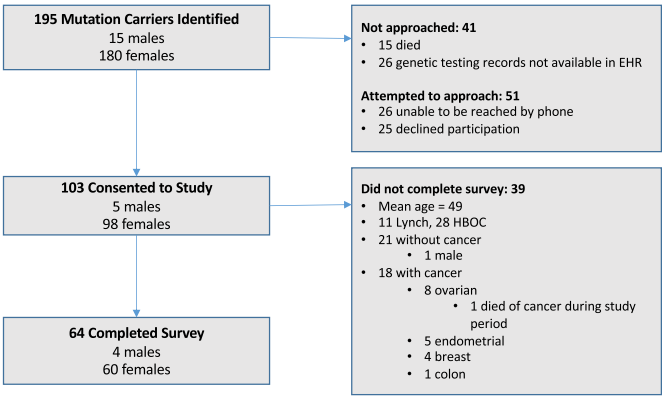

Fig. 1. Study design and flow chart, including information known regarding non-participants.

The average disclosure and CGT rates did not significantly associate with the participant's primary tumor site, stage, grade, or status; education level or annual income; strength of family communication; or feelings of preparedness to disclose results. However, participants with *BRCA1/2* mutations reported that first-degree relatives (both male and female) had significantly higher rates of CGT than did relatives of participants with LS or other/mixed mutations (49% vs. 33% vs. 19%, respectively, $P = 0.02$).

Participant relationship status was not associated with differences in average rates of disclosure. However, participants who were single or living with a partner reported that their first-degree relatives had higher CGT rates than did participants who were separated/divorced/widowed or participants who were married (57% vs. 47% vs. 32%, respectively, $P = 0.047$). We did not find any correlation between CGT rates and participants' income, educational level, insurance status, or ZIP codes.

The majority of participants reported feeling extremely comfortable (44%) or very comfortable (42%) discussing health information, and only 9 (14%) reported feeling not at all or moderately comfortable discussing health information. Extremely or very comfortable participants had higher average rates of disclosure to first-degree relatives than not-at-all or moderately comfortable participants (97%, 87%, and 59%, respectively, $P = 0.012$). Participant-reported communication strength within the family was similar to comfort in discussing health information, as 35 (55%) participants reported very good communication strength, 18 (28%) reported good communication strength, and 11 (17%) reported poor to acceptable communication strength. Disclosure correlated with the strength of family communications, though not significantly ($P = 0.05$). A summary of disclosure and testing rates by mutation, relationship, and comfort status is shown in Fig. 3.

Table 2 shows reasons participants relayed for not disclosing their genetic results to relatives. Young age of relatives was the most commonly cited reason for nondisclosure.

3.3. Materials to aid disclosure and CGT

Fifty-seven (89%) participants viewed the letter, 36 (56%) viewed at least one of the brochures, 35 (55%) viewed at least one website, and 34 (53%) watched at least one video. Over 50% of participants agreed or strongly agreed that each type of material would be helpful (regardless of whether or not they viewed the materials). However, no single type was perceived as significantly more helpful than the others, nor was any type significantly more or less helpful for disclosure to family members than for the participant's own understanding.

4. Discussion

In an academic gynecologic oncology genetic counseling practice, 97% of patients with HBOC or LS mutations reported that they

Table 1
Participant characteristics.

Characteristics	Total Participants (n = 64)	Participants with Cancer (n = 32)	Participants with No Cancer (n = 32)	P Value
Age (±SD)	53 (±14)	57 (±9)	49 (±16)	0.043
Race n (%)				1.000
Caucasian	62 (97)	31 (97)	31 (97)	
African American	2 (3)	1 (3)	1 (3)	
Gender n (%)				0.113
Female	60 (94)	32 (100)	28 (88)	
Male	4 (6)	0 (0)	4 (12)	
Mutations n (%)				0.028
BRCA1	20 (31)	11 (34)	9 (28)	
BRCA2	9 (14)	2 (6)	7 (22)	
MLH1	7 (11)	4 (13)	3 (9)	
MSH2	8 (13)	6 (19)	2 (6)	
MSH6	3 (5)	3 (9)	0 (0)	
PMS2	10 (16)	2 (6)	8 (25)	
RAD51D	2 (3)	0 (0)	2 (6)	
>1 Mutation	5 (8)	4 (13)	1 (3)	
Cancers n (%)			N/A	N/A
Ovarian	15 (23)	15 (47)		
Uterine	10 (16)	10 (31)		
Colon	3 (5)	3 (9)		
>1 Primary	3 (5)	3 (9)		
Cancer Treatments: n (%)			N/A	N/A
Chemotherapy Only	1 (2)	1 (3)		
Surgery Only	9 (14)	9 (28)		
Chemo/Surgery/Radiation	22 (34)	22 (69)		
Grade n (%)			N/A	N/A
1	8 (13)	8 (25)		
2	4 (6)	4 (13)		
3	13 (20)	13 (41)		
4	4 (6)	4 (13)		
Stage n (%)			N/A	N/A
I	15 (23)	15 (47)		
II	3 (5)	3 (9)		
III	11 (17)	11 (34)		
IV	3 (5)	3 (9)		
Risk-Reducing Procedure with No Cancer:		N/A		N/A
BSO	5 (8)		5 (16)	
Hyst + BSO	7 (11)		7 (22)	
Bilateral Mastectomy	2 (3)		2 (6)	
Bilat Mastectomy + BSO	1 (2)		1 (3)	
Hyst + BSO + Bilat Mast	1 (2)		1 (3)	

N/A: Not applicable.
Missing data: Cancers (n = 1), Grade (n = 3).

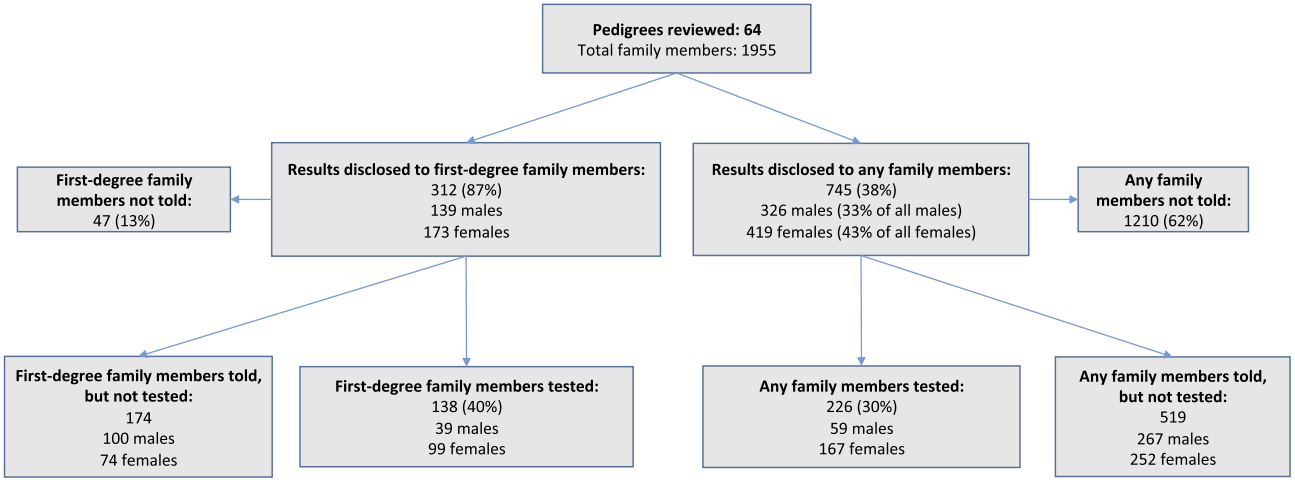

Fig. 2. Participant-reported disclosure and cascade genetic testing rates.

disclosed results to one or more relatives, most within six months of diagnosis. Although 87% disclosed results to all first-degree relatives, only 40% disclosed to all relatives in their pedigrees. Disclosure is most effective when relatives follow through with CGT. Our patients reported that 40% of at-risk first-degree relatives and 30% of all at-risk relatives underwent CGT. The highest CGT

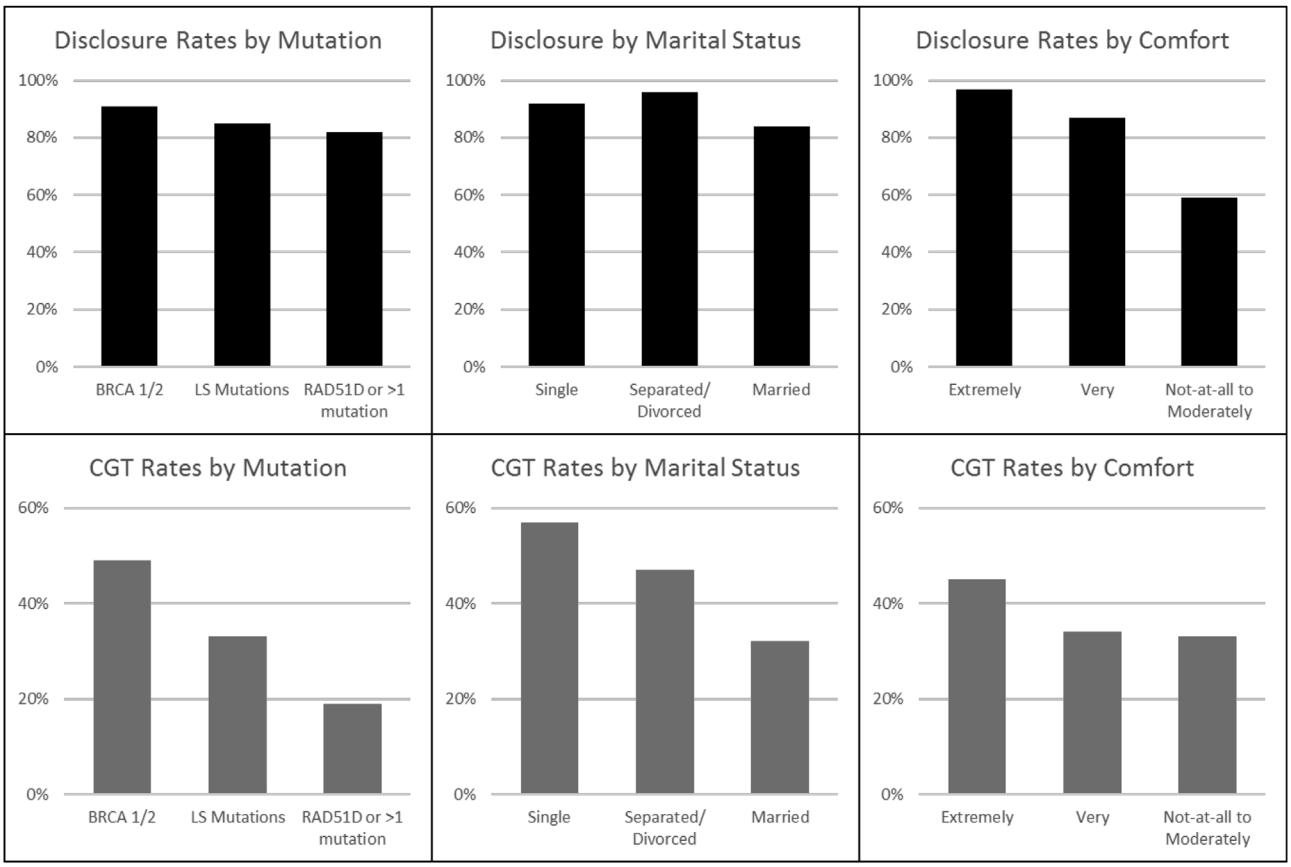

Fig. 3. Disclosure and cascade testing rates by specific germline mutations, relationship status, and comfort disclosing.

Table 2
Participant examples given for deciding against disclosure of mutation status to family members.

Participant-Reported Reason for non-disclosure	n
Family Member Too Young	18
Family Does Not Get Along	7
Concern About The Cost Of Genetic Testing	5
I Don't Want To Burden My Family	4
I Rely On Other Family Members To Disclose Mutation to Others	4
Family Member Too Old	3
I Don't Think Family Members Can Emotionally Handle The Information	3
My Family Members Asked Not To Be Told	2
I Don't Have Regular Contact With My Relatives	1
I Don't Know The Contact Info For My Relatives	1
I Didn't Understand my Relative's Risk	1
I Have Never Told A Relative That I Have Cancer	1

rates were in HBOC families, and women underwent CGT at higher rates than men. These results suggest that patients with HBOC or LS mutations understand the importance of disclosing mutation status to relatives, but barriers prevent family members from undergoing CGT.

In the United States, both oncologists and genetic counselors have relied on patients to disclose genetic testing results and encourage CGT. The high disclosure rates we identified suggest that this model remains adequate for disclosure. However, our results reveal four potential actionable barriers to CGT among first-degree relatives. First, we noted mutation-specific differences, as participants with *BRCA*-pathway mutations reported higher CGT rates than those with LS-associated or other/mixed mutations (even with similarly high disclosure rates). This finding may reflect the greater awareness of breast cancer risk and *BRCA1/2* among the general population. Continued education and public awareness regarding LS, cancer risk, and the potential for risk-reducing interventions is important. Future studies should directly assess family members' awareness of LS-related cancers.

Second, gender of family members affected the CGT rate of both first-degree and all relatives. Because we did not inquire about intent for testing in the future, the low rate for men may indicate that men delay, but still obtain, testing. Alternatively, this finding could indicate a lack of awareness that the HBOC and LS autosomal dominant mutations are not sex-specific. Thus, gender-specific education materials, particularly education aimed at male family members, may be helpful.

Third, relationship status of the patient correlated with CGT rates, as single participants reported higher rates of CGT than married participants. Previous studies have suggested that, compared to single patients, married patients are less likely to have frequent or detailed discussions of risk with blood relatives [7]. Although our finding warrants exploration in further studies, the focus should be on improving CGT rates for all at-risk blood relatives. Providers should stress to patients that their blood relatives are those at highest risk of inheriting a cancer-causing germline mutation.

Fourth, family dynamics appeared to affect disclosure and CGT rates. Not surprisingly, participants with lower levels of comfort disclosing information told significantly fewer first-degree relatives about their testing results than did those with higher levels of comfort. CGT rates also decreased as participant comfort with disclosing decreased, but these differences were not significant. Similar trends, though not significant, were present regarding communication strength within families. This underscores the fact that family members besides the proband can play a key role in CGT

and highlights the importance of ensuring that the quality and quantity of information disclosed to the patient can hold up throughout multiple family discussions. Providing standardized, validated disclosure instruments may facilitate discussion of genetic risk within families. Pre-visit screenings that survey patients about strength of family communication could be a way to identify educational needs of specific patients and their family members.

Although we did not directly assess this factor, patient recollection of information is another potential barrier to disclosure and CGT. Previous studies indicate that patients remember, at best, half of the information they receive at genetic counseling visits. Patients then relay mostly incomplete and inaccurate information to their family members, who only recall about one-third of the counseling information accurately [13,15,17]. Thus, relatives are likely to be far from fully informed of their cancer risk and the available preventative options. Such poor transmission of information may explain our finding that, despite high disclosure rates, reported CGT rates were low. Thus, our reliance on patient-driven cascading with little support and follow-up from providers is likely a major barrier for CGT in the United States.

A few studies have reported on efforts to overcome these barriers. Outside the United States and in non-gynecologic subspecialties, physicians have explored methods to support and standardize disclosure. For example, clinicians provide letters and educational material to relatives, either directly via mail/email or through patients, explaining the risks and recommendations associated with germline mutations. A handful of studies report that standardized letters almost double CGT rates in families [19–22], likely because families have a greater understanding of their risks and are more informed to pursue preventative measures. A committee opinion by the American Congress of Obstetricians and Gynecologists [23] promotes using family letters, but how well practices implement this tool has not been determined.

Our study examined four types of materials physicians could use to aid patients in disclosing germline mutation risks to relatives: letters, brochures, websites, and videos. Although participants generally believed that all of these materials would help them understand their mutations and cancer risk and disclose the information to relatives, more participants viewed the letter than the other materials, potentially indicating greater patient utilization of a letter format. Further studies are needed to identify and test strategies to improve dissemination of accurate information to family members. Given that standardized letters can be used to highlight key points regarding risk, they are reasonable first measures to implement into clinics to potentially improve CGT rates. Additionally, studies should explore the impacts of health care setting (academic versus community), race, gender, geographic location, and socioeconomic factors on disclosure and CGT. Although we found no correlation between CGT rates and income, educational level, insurance status, or ZIP codes of each survey participant, we did not obtain such details regarding their family members. Future studies should assess the effects of geographic barriers on CGT rates.

Limitations of this study include its small population size, retrospective design, subjective nature of participant survey responses, lack of input from relatives, and inability to assess the exact content of patient disclosure to relatives. Because relatives may not tell patients that they underwent testing, our patient-reported CGT rates may underestimate true CGT rates. Ideally, future studies should also survey relatives to further define barriers to CGT and determine whether relatives who test positive for germline mutations receive appropriate follow-up and preventative care. Another limitation of this study is that it included both patients receiving treatment for cancer and those referred for high genetic risk but not a cancer diagnosis. Although sub-analyses showed no differences in demographics, survey response rate, disclosure rate, or CGT rate between these two groups, these two populations should be considered separately in future studies, as their experiences and barriers to disclosure and CGT may differ. We also acknowledge that the majority of participants were Caucasian. African-American and other minority patients may face unique barriers to disclosing testing results and CGT [24]. Thus, future studies should address racial and ethnic differences in testing and identify strategies that are most effective to improve disclosure and CGT rates in diverse populations.

The participants in this study had at least enough access to care to obtain treatment, and they were seen at a large academic center with an embedded genetic counselor as part of routine cancer care. This study may not generalize to patients with barriers to access or those seen in a clinic without a genetic counselor. However, regardless of setting, genetic testing in cancer care is increasingly focused on assessing the patient's tumor biology and therapeutic options, with less focus on standardized pedigrees required for testing, as has commonly been done with genetic counselors. To calculate a denominator for CGT rates in this study, we were able to easily identify the number of at-risk first-degree relatives by pedigree review. A pedigree review can provide a powerful visual representation to the cancer patient and provider—at quick glance elucidating the ages and numbers of family members who carry a 50% risk of inheriting a mutation. In this study, the most commonly noted reason for lack of disclosure was young age, which again reflects appropriate counseling regarding mutations that carry an adult-onset cancer risk. Strategies to efficiently incorporate pedigree review and document follow-up of family member testing in cancer surveillance visits could help improve CGT rates.

This study did not focus on clinician barriers. Furthermore, concerns over privacy laws such as the Health Insurance Portability and Accountability Act and the Genetics Information Nondiscrimination Act limit providers' ability to help patients and their relatives overcome the barriers they face [25]. Defining a usable metric for clinicians to document CGT could help providers educate their patients, assess and work to overcome barriers, and find an acceptable strategy to help standardize guideline-based care of patients and relatives.

In conclusion, our study is in line with previous literature documenting a large gap between disclosure of genetic testing results and subsequent testing among relatives of patients at risk for HBOC and LS. Our survey indicated that current genetic counseling practices provide sufficient support to allow patients to disclose genetic test results to family members but insufficient support to ensure that family members undergo CGT. Given the potential of CGT to prevent cancer, we should begin testing strategies to narrow this gap. Successes in other countries and subspecialties suggest that routine use of letters would be acceptable to patients and families and would increase CGT rates, and this strategy is encouraged by the American Congress of Obstetricians and Gynecologists. Future studies should focus on clinician barriers to reaching family members of probands and should be carried out in more diverse settings. Additionally, studies should develop gender- and mutation-specific letters and other materials and evaluate their impacts on CGT rates. We hope this study spawns interest in rapid, pragmatic implementation trials to improve CGT rates.

Author contributions

NG: data collection, initial drafting/final editing, critical analysis.
TB: data collection, drafting, critical analysis.
SS: data collection, drafting, critical analysis.
AL: data collection, research assistance, critical analysis.
MM: IRB submission, conception, survey design.
JL: statistical analysis, critical analysis.

RT: critical analysis, survey design with Dissemination and Implementation Core.

KF: critical analysis.

LSM: critical analysis, final editing.

DM: critical analysis.

PT: critical analysis.

MP: critical analysis.

GC: conception, critical analysis, drafting/final editing.

AH: conception, data collection, statistical analysis, critical analysis, drafting/final editing, supervision.

Declaration of competing interest

Drs. Griffin, Buchanan, Smith, Liu, Tabak, Fuh, Massad, Colditz, and Hagemann, and Ms. Leon have nothing to disclose. Dr. Mutch reports personal fees from Clovis Oncology and Astra Zeneca that are outside the scope of this work. Dr. Thaker reports personal fees from Abbvie, Astra Zeneca, Stryker, Lovance, Clovis, and Unlease; personal fees and other from Celsion and Tesaro; and grants and personal fees from Merck; all are outside the scope of this work. Dr. Powell reports personal fees from AstraZeneca, Eisai, Merck, Tesaro, Clovis Oncology, and Roche, all outside the scope of this work.

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