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ORIGINAL RESEARCH

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Effects of cancer type and sex on genetic testing for clinician recommendation and uptake

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Abstract

This study investigated reasons for lower-than-expected uptake of germline genetic testing compared to national guidelines amongst adult patients with cancer, self-reporting clinician recommendation for genetic testing. Cross-sectional survey of 596 patients with a personal history of cancer, responded about their cancer diagnosis, physician recommendation for and status of genetic testing and demographics. Adjusting for potential confounding factors (cancer type, education, income and insurance status) male sex significantly decreased odds of receiving a clinical recommendation for genetic testing (Odds Ratio: 0.06; 95% Confidence Interval: 0.04–0.10). Females, with a diagnosis of breast cancer, were more likely to receive a recommendation than other cancer types (64.8% *vs.* 90.9%, $p < 0.001$). Participants who received a physician recommendation were significantly more likely to receive genetic testing ($p < 0.001$). Clinician recommendation is an important driver of genetic testing, necessitating efforts to increase clinician recommendations, particularly for males and patients with cancers other than breast.

Keywords

Adults; Cancer; Genetic testing; Genetic risk; Breast cancer; Prostate cancer; Adherence

1. Background

Genetic testing can provide clinically actionable information to aid in the detection, prevention and treatment of hereditary cancers [1, 2]. Many eligible patients do not obtain clinically indicated testing [3–5]. Groups with particularly low rates of genetic testing for patients that are biologic male [4, 6–9], underinsured [6, 7, 10, 11], belong to a racial/ethnic minority group [5, 6, 12–16], or have a cancer other than breast [3, 6, 17–19]. Patient barriers to testing include lack of understanding of the clinical usefulness, cost concerns and lack of clinician recommendation.

Several studies show that clinician recommendation drives genetic testing uptake [1, 3–5, 8, 12, 17, 20–24] and conversely, few patients seek patient-initiated testing without a referral [25]. Many patients who are eligible for testing are not receiving a recommendation from their clinicians despite national guidelines to do so [3, 4, 23]. Recommendations are reported at consistently higher rates for patients who are biologically female [7, 8, 18], diagnosed with breast cancer [6, 8, 26], or colorectal cancers [12, 17, 18]. Additionally, recommendation and uptake rates differ within cancer predisposition syndromes for example, within Lynch-associated cancers, females are tested at a higher rate [17, 18].

Most prior studies examine the association between clinician recommendation and testing uptake in homogenous groups such as a single type of cancer (*e.g.*, breast [8, 16, 26], prostate [3, 27, 28]), or patient risk profile (*e.g.*, syndromic cancers [6, 8, 12, 16–19]). The purpose of this study was to examine the frequency of clinician recommendation and its association with patient-reported genetic testing within a novel sample of patients diagnosed with multiple cancer types in a single academic healthcare system.

2. Measures

We used both previously validated and novel measures to assess perceived and reported benefits and barriers to genetic testing. Respondents' self-reported receipt of genetic testing with a single item: (1) Yes, (2) No, (3) Not sure. Categories two and three collapsed to "no" to simplify analysis. We queried whether any clinician recommended genetic testing using four response categories: (1) Yes, they recommended genetic testing for me; (2) No, they didn't think I needed genetic testing; (3) No one has talked about genetic testing with me; (4) I'm not sure. For analysis, response options two, three and four, were collapsed into one category.

Descriptive variables collected included sex (assigned at birth and identification), age (current and at diagnosis), education (collapsed into three categories), income (collapsed into three categories), insurance status (public: Medicare, Medicaid, Tri-care, Veterans Affairs, Indian Health; private:

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employer-funded; other), number of biological children, race/ethnicity (select all that apply), employment status, cancer type(s), along with treatment(s) received. Regardless of sex assigned at birth, all participants were shown all cancer types (bladder, breast, cervical, colon, endometrial, lung, melanoma, ovarian, pancreatic, prostate, rectal and ten others) and patients could report multiple primary cancers. Due to cancer type overlap in hereditary cancer syndromes (*e.g.*, ovarian cancer associated with *BRCA1/2* mutation and Lynch Syndrome), we dichotomized cancer types into gastrointestinal (GI) (colon, rectal and pancreatic) and non-GI, to examine potential interaction effects outside of *BRCA1/2*-related cancer types.

3. Methods

We conducted a cross-sectional survey to understand barriers and drivers for genetic testing uptake in a one-arm sample population of English-reading patients with a personal history of cancer. The sample was obtained through the University of Michigan patient registry, DataDirect, which enables access to clinical data such as diagnoses, procedures and laboratory results for more than 4 million unique patients.

Inclusion criteria were defined as patients of any sex, over 18 years, who completed an inpatient or outpatient encounter with any clinician at Michigan Medicine between 01 January 2019 and 15 February 2021, whose medical record includes an International Classification of Diseases (ICD)-9 or ICD-10 code indicating a diagnosis of one of the following cancers which align with 2019 National Comprehensive Cancer Network (NCCN) criteria for germline genetic testing (1) breast cancer under the age of 50, (2) prostate cancer under the age of 50, (3) metastatic prostate at any age, (4) colorectal cancer at any age, (5) endometrial cancer at any age, (6) ovarian cancer at any age, and (7) pancreatic cancer at any age. These cancers were selected due to national guidelines for genetic testing uptake during the enrollment period. The NCCN re-evaluates the criteria annually and components of the criteria used to select the study population have been in place for varying time periods before 2019, however, all were in place in 2019 [29]. We did not collect family history or age of diagnosis to strictly use NCCN guidelines for genetic testing eligibility, but based eligible cancer types off of NCCN criteria [29, 30]. Breast, pancreatic and ovarian cancer types in our study are consistent with NCCN (breast diagnosed under 50, pancreatic and ovarian cancer types which recommend testing at any age of diagnosis). All participants were selected by an algorithm based on this criteria, that included a diagnosis before 50-years for breast and prostate cancers only. Participants could report one, or more, cancer types. The final sample of participants was 797, 596 of which answered the questions regarding receiving a recommendation for (n = 596), receiving genetic testing (n = 581), and reported a NCCN eligible cancer type for hereditary genetic testing in 2019, that would be eligible for a related clinical trial (n = 596).

An email invitation to a Qualtrics^{XM} survey was sent to patients regardless of genetic testing status. No reminders were sent. Those who signed written consent were enrolled and offered $10 for survey completion. In the first phase of recruitment, patients were invited regardless of their genetic testing status, however those who reported being tested were overrepresented in our sample population. We therefore added one question to the eligibility screener in the second phase to exclude individuals who had received genetic testing. During the second phase we recruited 512 individuals, of which 171 persons were excluded because they had received genetic testing, cancer type unknown. The final sample of participants from both phases who completed both the questions about recommendation for and receipt of genetic testing was 596. No participants withdrew consent to participate.

Demographic variables, cancer type and genetic testing characteristics were summarized by frequency. Respondents were asked to report their sex assigned on their original birth certificate as well as their gender identity. Too few respondents identified as transgender, non-binary, intersex or other sex for analytic power. Therefore, sex assigned at birth (biologic sex) was dichotomized as “male” or “female”. Associations between demographic and cancer characteristics along with the recommendation for and receipt of genetic testing were assessed using logistic regression after collapsing response options “no” and “I don’t know” into “no”.

Multivariable logistic regression assessed the association between demographic and cancer characteristics motivated from previous literature and the odds of being recommended genetic testing by their clinician. Similarly, multivariable logistic regression assessed the association between demographic and cancer characteristics and the recommendation for genetic testing with the odds of receiving genetic testing.

The primary outcome of participant-reported recommendation of genetic testing (yes/no) was compared between male and female sexes with biologic sex-associated cancer types (breast, cervical, endometrial/uterine, ovarian, prostate). These cancer types could indicate testing for Hereditary Breast Ovarian Cancers or Lynch syndrome associated cancers. Associations between GI and non-GI cancers were examined to look for correlations amongst participants who are male or female, excluding those with breast cancer, as prior research has shown a strong relationship between genetic testing recommendation, and uptake within breast cancer, including a sample with male and female participants. In all analyses, gastrointestinal (GI) cancer is defined as colon, rectal or pancreatic cancer; Lynch-associated cancer types are defined as bladder, colon, endometrial, kidney, liver, ovarian, pancreatic, rectal and stomach.

Given the pilot and exploratory nature of the study, we did not control for multiple comparisons. Data was analyzed using R and SPSS v.28. The dataset supporting this study is available at DOI: https://doi.org/10.7302/59xr-c178.

4. Results

An email invitation to a Qualtrics^{XM} survey was sent to 3000 patients from an academic hospital (of these, 166 emails were undeliverable). No reminders were sent. This study population excluded those who did not respond to either genetic testing question (receiving testing or a recommendation, nor had a cancer type with NCCN guidelines for genetic testing as of 2021. Of the 596 survey respondents, the majority were

female (69.6%), white (87.1%) and over the age of 45 (74.5%). The majority also reported an annual income over $75,000 (57.0%), private (employer-funded) insurance (65.3%), and a bachelors or advanced degree (74.5%). In terms of cancer history, the majority had a non-gastrointestinal cancer (85.6%), most commonly breast cancer (44.5%), and were diagnosed less than 5 years prior (62.8%). The description of the study population is found in Table 1.

Overall, 65.4% of the sample reported receiving a clinician recommendation for genetic testing. Males were less likely to receive a recommendation than females ($p < 0.001$) (Table 2). After adjusting for potential confounding factors such as cancer type, education, income, insurance status, the effect of male *vs.* female sex remained statistically significant (OR: 0.06; 95% CI: 0.04–0.10) (Table 2).

Male and female participants with Lynch-associated cancers reported recommendations at statistically significantly ($p = 0.004$) different rates, with males being less likely. —Fifty-three percent of males with a Lynch—associated cancer type received a recommendation for genetic testing (n = 26/49; data not shown), whereas 74.4% of females with a Lynch-associated cancer type were recommended to receive genetic testing (n = 128/172, 74.4%; data not shown). This is even true when looking at GI-associated cancer types (OR: 0.06; 95% CI: 0.02–0.17) (Table 3).

Looking at biologic sex-associated cancer types (Table 1), 14.7% of males and 84.9% females reported having received a genetic testing recommendation ($p < 0.001$; data not shown).

Within females with breast cancer, 90.5% received a genetic testing recommendation from a clinician compared to 73.2% of females with all other cancers ($p < 0.001$; data not shown).

Overall, 62.8% of the sample reported receiving genetic testing (Table 1) which differed by sex (Table 4) and cancer type (data not shown). In univariate analyses, the odds of a male receiving genetic testing was 0.03 times that of a female (CI: 0.02–0.05). After adjusting for potential confounders such as cancer type, education, income, insurance type, sex affects remained essentially unchanged (OR: 0.08; 95% CI: 0.04–0.15).

Respondents who reported a clinician recommendation for genetic testing were significantly more likely to report receiving genetic testing (Table 4) ($p < 0.001$). Specifically, of the 390 respondents who received a clinician recommendation, 351 (90.0%) reported receiving genetic testing, compared to 10 (2.7%) who reported receiving genetic testing without a referral. Adjusting for age, biologic sex, GI-associated cancer types, education, income and insurance type, clinician recommendation for genetic testing is significantly associated with testing uptake (OR: 104.3; 95% CI: 40.9–266.0) (data not shown). The interaction between clinician recommendation and sex was significantly associated with testing uptake.

5. Discussion

While prior studies show genetic testing uptake is correlated with clinician recommendation [1, 3–5, 8, 12, 17, 20–24]. This cross-sectional survey found that males were less likely to receive a recommendation for genetic testing and less likely to complete genetic testing than females adjusting for confounders and cancer type, similar to Vysotskaia *et al.* [23]. Additionally, consistent with prior research, clinician recommendation strongly associated with completing genetic testing amongst both sexes [4, 8, 23, 31].

Our finding that females receive recommendations more frequently than males is consistent with prior literature [4, 6–9]. Germline genetic testing for breast cancer has been clinically available for almost 30 years, and most patients and providers have heard of Hereditary Breast Ovarian Cancer Syndrome associated with pathogenic germline variants in *BRCA1/2* [32]. After breast cancer, referral rates were next highest for patients diagnosed with colorectal cancers [12, 17, 18]. Lynch Syndrome is the most common hereditary colorectal cancer syndrome with a population prevalence of 1 in 279 (comparable to *BRCA1/2*); yet although genetic testing for these genes has also been available since the 1990s [33]; fewer patients and clinicians have heard of Lynch Syndrome. We found sex differences with females more likely than males to be referred for genetic testing, even when limiting the sample to patients with Lynch-associated and GI-associated cancers [6, 7, 17, 18] where national testing guidelines do not differ by sex. This is also consistent with Scott *et al.* [8] and a systematic review by Sharaf *et al.* [18] that found that females are more likely than males to receive a recommendation and undergo testing for Lynch Syndrome. Thus, clinicians are more likely to make a recommendation for genetic testing based on both the sex of the patient as well as their diagnosis, even within this academic-based healthcare system.

The observation that males were less likely to receive a recommendation for or complete genetic testing is consistent with prior studies [4, 6–9]. "The observed rates of testing amongst those who received a recommendation were qualitatively different for males and females, 59.0% *vs.* 94.6% respectively. This suggests efforts are needed to better encourage males to follow through with testing recommendations from their clinicians". Also, our findings show the association of clinician recommendation and patient testing uptake for both male and female patients held across multiple cancer types whereas most prior studies only examined individual cancer types or specific cancer predisposition syndromes (breast [8, 19, 26], Lynch syndrome [6, 17, 18], ovarian [10, 13, 14, 19, 21], prostate [3, 27, 28]).

5.1 Clinical implications

Taken together, our findings indicate a need to increase the rate of genetic testing recommendations from clinicians for eligible males as they are less likely to get genetic testing, yet equally likely to respond to clinician recommendation. Although clinician recommendation rates are particularly high for females with breast cancer, recommendation rates for females with other cancer types merits attention [12, 17], as well as females with intersectional identities, such as race, sexual orientation, gender identity or gender presentation [5, 12, 34]. Clinicians could receive education on current American Medical Association guidelines for inclusive language when making clinical recommendations for those who do not identify as cisgender, heterosexual or monogamous to ensure referrals are placed in visits with high clinician-patient

TABLE 1. Participant characteristics, N = 596.

Demographics	N = 596 (100%)
Sex	
Male	178 (29.9%)
Female	415 (69.6%)
Transgender	2 (0.3%)
Do not identify as female, male or transgender	1 (0.2%)
Race	
Black or African American	13 (2.2%)
Hispanic/Latinx	12 (2.0%)
Middle Eastern or North African	10 (1.7%)
Multiracial	16 (2.7%)
Other (includes American Indian or Native American, Alaskan Native, Native Hawai'ian or Other Pacific Islander, Asian or Asian American)	25 (4.2%)
White or European American, non-Hispanic	519 (87.1%)
Missing	1 (0.2%)
Age	
≤45	151 (25.3%)
46–65	265 (44.5%)
≥66	179 (30.0%)
Missing	1 (0.2%)
Education	
≤Bachelors	151 (25.3%)
Bachelor's Degree	193 (32.4%)
Advanced Degree	251 (42.1%)
Missing	1 (0.2%)
Income	
<$30,000	38 (6.4%)
$30,000–$74,999	143 (24.0%)
>$75,000	340 (57.0%)
Missing	75 (12.6%)
Health Insurance Type	
Public/government	197 (33.1%)
Private	389 (65.3%)
Other	7 (1.2%)
Missing	3 (0.5%)
Years Since Cancer Diagnosis	
<2 yr	145 (24.3%)
3–5 yr	229 (38.5%)
6–10 yr	131 (22.1%)
>10 yr	91 (15.4%)
Cancer Types, could select >1	
Breast	265 (44.5%)
Cervical	5 (0.8%)
Colon	32 (5.4%)
Endometrial	26 (4.4%)
Ovarian	109 (18.3%)

TABLE 1. Continued.

Demographics	N = 596 (100%)
Pancreatic	46 (7.7%)
Prostate	149 (25.0%)
Rectal	9 (1.5%)
Other cancer Types Reported	96 (16.1%)
Cancer syndromes	
Biologic Sex associated	534 (89.6%)
BRCA-associated	546 (91.6%)
Gastrointestinal (GI) associated	86 (14.4%)
Lynch Syndrome associated	221 (37.1%)
Genetic testing recommended	
No	206 (34.6%)
Yes	390 (65.4%)
Received genetic testing	
No/Not sure	216 (37.2%)
Yes	365 (62.8%)
Missing	15 (2.5%)

Descriptive statistics of all survey respondents answering questions of receiving genetic testing or a recommendation for testing, as well as reporting a cancer type with NCCN guidelines for genetic testing.

TABLE 2. Clinician recommendation for genetic testing by sex, N = 596.

	Patients received clinician recommendation for genetic testing		
Sex at birth*	No/Not sure	Yes	Total
Male	140 (78.2%)	39 (21.8%)	179
Female	66 (15.8%)	351 (84.2%)	417
Total	206 (38.1%)	390 (62.8%)	596

* χ^2 $p < 0.001$.

TABLE 3. Association of clinician recommendation on genetic testing uptake within GI-associated cancers, N = 596.

		Reported recommendation for genetic testing		
Sex at birth	Reported a diagnosis of a GI-associated cancer	No/Not sure	Yes	Total
Male*				
	No	123 (89.8%)	14 (10.2%)	137
	Yes	16 (40.5%)	25 (59.5%)	42
	Total Male	140 (78.2%)	39 (21.8%)	179
Female*				
	No/Not sure	57 (15.3%)	316 (84.7%)	373
	Yes	9 (20.5%)	35 (79.5%)	351
	Total Female	66 (15.8%)	351 (84.2%)	417
Total*				
	No/Not sure	180 (35.3%)	330 (64.7%)	510
	Yes	26 (30.2%)	60 (69.8%)	86
Total		206 (100%)	390 (100%)	596

This includes those who responded to both questions regarding the recommendation for and receipt of genetic testing.
* χ^2 $p < 0.001$ *within group. GI: gastrointestinal.*

TABLE 4. Association of clinician recommendation on genetic testing uptake (N = 581).

		Reported genetic testing status		
Sex at birth	Clinician recommended genetic testing	Untested	Tested	Total
Male*				
	No/Not sure	136 (97.8%)	3 (2.2%)	139
	Yes	16 (41.0%)	23 (59.0%)	39
	Total Male	152 (85.4%)	26 (14.6%)	178
Female*				
	No/Not sure	45 (86.5%)	7 (13.5%)	52
	Yes	19 (5.4%)	332 (94.6%)	351
	Total Female	64 (15.9%)	339 (84.1%)	403
Total*				
	No/Not sure	181 (94.8%)	10 (5.2%)	191
	Yes	35 (9.0%)	355 (91.0%)	390
Total		216 (100%)	365 (100%)	581

This includes those who responded to both questions regarding the recommendation for and receipt of genetic testing.
** χ^2 $p < 0.001$ within group.*

rapport. Efforts to promote guideline-concordant recommendations for genetic testing could include both clinician and patient-facing interventions. For clinicians, this may include post-graduate continuing medical education or maintenance of certification requirements in current genetic testing guidelines, evidence-based approaches to encourage testing completion. Clinicians could also benefit from developing evidenced-based approaches to identify eligible patients and communicate the value of genetic testing to increase the likelihood of testing completion for probands and their families such as a digital tool developed to provide example necessary concluded that the knowledge of "medically actionable" [2]. Clinicians could also benefit from best practice alerts in electronic records could include conversation starters for specific diagnoses in conjunction with quality improvement programs that decrease barriers to referrals for genetic counseling and testing, increase motivation to test, or improve coordination of care efforts across. For patients meeting genetic testing, guidelines, secured-portal or text messages, with conversation starters, to empower advocating for testing with their clinicians as well as links to patient-initiated testing options through clinical laboratories that include information about potential out-of-pocket costs. Independent clinical testing laboratories with relationships to specific clinicians or clinics could provide test results within the patient's electronic medical record with referral recommendation for genetic counseling services, cascade testing or other testing other genes. As noted by Scott *et al.* [8], "Among patients with high genetic risk, clinicians' recommendations, potential treatment implications, and protections against discrimination were motivating factors to undergo genetic testing, but fewer than half recalled clinicians providing all this information, and this did not improve over time" [8] demonstrating an immense need for broad public health education initiatives.

Additionally, electronic medical records are inconsistent in containing a complete family health history, limiting appropriate referral to germline testing. Increasing adherence to updated family cancer history could improve adherence to NCCN guidelines.

5.2 Study limitations

There are several limitations to this study. First, patients self-reported their clinician's recommendation and testing received, sometimes years after their diagnosis, and this may have limited the accuracy of their recall [35, 36]. Prospective studies assessing clinician recommendations in real time, or near real time, would be helpful in validating our results as the validity of self-reported genetic testing has previously been questioned [3]. Second, our sample population was homogenous with regard to race/ethnicity and income. Despite amending the inclusion criteria to oversample those without breast cancer, the final sample had a high (44.5%) proportion of participants with breast cancer, perhaps driving recommendation rates. Third, all of our participants were recruited from a single academic health system with a high rate of insurance coverage. Fourth, sample sizes for some cancer types, particularly amongst males, are small, limiting generalizability. Studies examining the generalizability of our findings to other institutions and more diverse populations are needed. Using more objective methods of ascertaining clinician recommendation (*e.g.*, notes from clinician encounters) and genetic testing (*e.g.*, medical record verification) would help strengthen the validity of their association. Finally, response bias may have influenced our findings as only 26.2% of those invited participated, 69.64% were female, and this group may have differed from the non-responders. Additionally, cancer types in our sample population do not mirror the general population incidences (*i.e.*, ovarian cancer is far less common in the general population than in our sample population).

One limitation of our analyses is that NCCN guidelines

regarding genetic testing have shifted over the years. For example, NCCN version 1.2020 (released December 2019) first recommended multi-gene panel testing for all patients with a personal history of pancreatic cancer (or those with a first degree relative). This was updated in version 1.2022 to recommend testing for people with a family history of pancreatic cancer. While many NCCN guidelines include family cancer history to determine eligibility for germline testing, this sample may have excluded participants who may have been eligible based on family history. Future studies could include a history of cancer in the family to increase confidence in a genetic testing recommendation. This study team has collected complete family cancer histories for the related clinical trial to improve assessment for hereditary cancer risk.

6. Conclusions

Sex differences in uptake of germline genetic testing for cancer susceptibility may be attributable to differences in clinician recommendation. Clinicians are recommending genetic testing less for males than females and less for cancers other than breast. The impact of a clinician recommendation on testing uptake is substantial and the impact is similar between sexes and cancer types suggesting focused efforts are needed to promote increasing clinician recommendations particularly for men and cancers other than breast.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author. The dataset supporting this study is available at DOI: https://doi.org/10.7302/59xr-c178.

AUTHOR CONTRIBUTIONS

ED, ENH, SA, JJG, EMS, LGH, STH, EB and KR—designed the research study. ED, ENH and EB—performed the research. ED, ENH, SA, EB, GC, KMK and KR—analyzed the data. ED, ENH, SA and KR—wrote the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The University of Michigan Medical School Institutional Review Board (IRBMED) approved contacting patients who met the eligibility criteria with the application HUM0019157. All participants signed an electronic consent form prior to enrolling in the study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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