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Article

ARTICLE

Germline Testing for Patients With *BRCA1/2* Mutations on Somatic Tumor Testing

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Abstract

Background: The National Comprehensive Cancer Network (NCCN) recommends germline testing for pathogenic *BRCA1/2* mutations identified by somatic tumor sequencing. The aim of this study was to explore whether patients at Stanford with somatic *BRCA1/2* mutations were recommended germline testing in accordance with NCCN guidelines.
Methods: We retrospectively collected all Stanford patients with *BRCA1/2* mutations found by tumor sequencing. Medical records were reviewed for each patient to identify those recommended germline testing. A multivariable logistic regression model was fit associating baseline characteristics with whether or not a recommendation was made.
Results: Of 164 participants, 51 (31.1%) had no recommendation for germline testing. Of the 97 available germline-testing results, 54 (55.7%) were positive for pathogenic *BRCA1/2* mutations. After adjusting for possible confounders, patients with genitourinary cancer (odds ratio [OR] = 0.03, 95% confidence interval [CI] = 0.00 to 0.03; $P = .003$), lung cancer (OR = 0.04, 95% CI = 0.01 to 0.21; $P < .001$), sarcoma (OR = 0.02, 95% CI = 0.00 to 0.14; $P < .001$), skin cancer (OR = 0.01, 95% CI = 0.98 to 1.03; $P = .002$), or "other" diagnoses (OR = 0.01, 95% CI = 0.00 to 0.16; $P < .001$) were statistically significantly less likely to be recommended germline testing compared with patients with breast or gynecological cancers.
Conclusions: Our study highlights the importance of provider education outside of the oncologic specialties typically associated with *BRCA*-related cancers and continued exploration of referrals to genetics for germline testing on the basis of somatic findings.

The application of genetics in cancer treatment and personalized care is rapidly becoming standard practice. Next-generation sequencing tumor profiling allows oncologists to identify acquired (somatic) mutations that further define and characterize cancer phenotypes. Clinical management in this setting is now guided by tissue of origin or specific tumor pathology, as well as individual molecular variations detected by tumor sequencing (TS). Somatic TS can uncover prognostic driver mutations and relevant biomarkers that may assist in tailoring treatment and identifying appropriate clinical trials (1). Molecular tumor diagnostic reports are becoming more actionable as the development of matched, targeted therapies continues. Another important outcome of TS is the potential secondary discovery of pathogenic germline alterations.

An estimated 5%–10% of all cancer diagnoses are thought to be attributable to hereditary predispositions (2–4). For ovarian cancer specifically, 18% of cases may be caused by germline mutations in the *BRCA1* or *BRCA2* genes (5). Hereditary breast and ovarian cancer (HBOC) syndrome and Lynch syndrome are the most common inherited cancer predispositions, but more than 300 distinct syndromes have been described (3). Consequently, for a statistically significant fraction of patients who undergo TS, somatic and germline variants will be indistinguishable. Paired tumor-normal analysis, involving simultaneous sequencing of tumor and normal tissue, is one way to distinguish somatically acquired changes from inherited germline mutations (6). For example, Mandelker et al. (6) reported 17.5% of patients with advanced cancer diagnoses had clinically

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actionable, inherited mutations (in genes of low, moderate, and high cancer risk) after performing tumor-normal sequencing. A separate study described nearly 16% of patients in their cohort as carrying pathogenic germline mutations after paired tumor-normal sequencing, half of which would not have been predicted by the patient's personal or family history (7). Although an oncologist's primary goal in ordering TS is often focused on the patients and their immediate medical treatment options, secondary findings affecting the patients and their relatives must also be accounted for. The intersection between somatic and germline testing overlaps, and these results not only have implications for the patient's future cancer risk and clinical care but also will affect additional family members and their respective cancer risks.

Paired tumor-normal sequencing can differentiate somatic and germline variants, but its implementation into standard practice remains challenging. First, sequencing two samples per patient is expensive. Second, the practical implication of acquiring a tumor specimen and a germline (usually blood) sample in an individual patient is often a barrier (1). Furthermore, insurance companies often do not reimburse germline investigations if the patient does not meet standard genetic testing criteria. Traditional guidelines indicating eligibility for germline testing include family history, age of cancer onset, pathologic tumor features, and previous cancer diagnoses (8–10). Accumulating evidence from genomic studies supports expanding the guidelines for genetic testing. In one study, 101 of 182 patients with inherited pathogenic mutations identified via tumor-normal sequencing would not have met germline-testing criteria (6). As a result, national guidelines are broadening their inclusion criteria to include those with particular TS results (11). In the absence of tumor-normal sequencing, the variant allele frequency (VAF) of a mutation within a tumor specimen may also serve as an indication of germline vs somatic status (8). Although VAF alone should not be used to infer germline status, the Association for Molecular Pathology, the American Society of Clinical Oncology, and the College of American Pathologists recently published recommendations stating that an allele found around a frequency of 50% within a tumor is considered suspicious for being associated with a germline source (10).

National recommendations advise that when a somatic pathogenic or likely pathogenic (P/LP) *BRCA1/2* variant is identified by TS, a referral should be made to genetics for counseling and germline testing. First published by the National Comprehensive Cancer Network (NCCN) in the *Genetic/Familial High-Risk Assessment: Breast and Ovarian* practice guidelines on September 19, 2016, and updated January 18, 2019, it currently states that a "*BRCA1/2* pathogenic/likely pathogenic variant detected by tumor profiling on any tumor type in the absence of germline pathogenic/likely pathogenic variant analysis" does meet criteria for germline *BRCA1/2* testing (12). Pathogenic *BRCA1/2* mutations have traditionally been associated with breast and ovarian cancer and, more recently, prostate and pancreatic cancers; however, the NCCN makes clear that this guideline applies to any tumor type. As such, it is essential for oncologists who treat patients in all specialties to be aware of this precedent if they are ordering TS. The purpose of our study was to assess how frequently patients with a P/LP *BRCA1/2* mutation on TS were recommended germline testing or referred to genetic counseling. Our study also sought to identify factors associated with referrals and recommendations and whether a higher *BRCA1/2* VAF within the tumor specimen was associated with a positive germline test. Finally, we evaluated whether recommendations or referrals for germline testing changed over time.

Methods

Data Collection and Study Design

Physicians at Stanford Healthcare currently use one of two NGS platforms to molecularly profile biopsied or resected tumors: a commercial send-out through Foundation Medicine (FM, Cambridge, MA) or an in-house test using the Stanford Tumor Actionable Mutation Panel. Databases from both platforms were queried from January 2013 to February 2019 for Stanford somatic tumor reports that had identified known P/LP *BRCA1/2* variants. For cases with multiple existing reports due to successive biopsies or surgeries, the earliest report was used. Variables collected included the report date, pathogenicity status, *BRCA1* vs *BRCA2*, the coding DNA and protein reference sequence, VAF, and the resected specimen site.

A retrospective chart review was performed under approval of Stanford's institutional review board. Consultation notes were assessed for evidence of referrals to genetic counseling or recommendations for germline testing. An individual was considered to have been referred or recommended if a genetics consultation note was identified, a referral to genetics was placed, any recommendation for germline investigation was documented within a clinician's note, or indication of prior germline testing was noted. Additional details on cohort selection are provided in the Supplementary Methods, available online. Basic demographic information was collected and included sex, race, past and current diagnoses, histology and stage, age of first hereditary-related cancer diagnosis, and relevant family history. Head and neck cancers, central or peripheral nervous system tumors, and one perivascular epithelioid cell tumor were grouped under the "other" tumor type.

Statistical Analysis

Descriptive statistics were used to describe baseline characteristics and clinical action based on the tumor report of the overall cohort. Continuous and categorical variables were reported as median (range) and count (percent age), respectively. Sankey diagrams were created to display the trajectory of genetic counseling referrals and germline-testing recommendations by tumor group, as well as available germline-testing results by tumor group.

A multivariable logistic regression model was fit to whether or not a patient was recommended germline testing as a function of sex, ethnicity, age of cancer onset, cancer stage, tumor group, VAF, and an indicator for whether or not TS was conducted before the NCCN guideline publication. Similar methods were used to assess the association between baseline characteristics and *BRCA1/2* germline result. An optimal threshold for VAF was calculated to best categorize positive and negative germline results. Odds ratios (OR) and 95% confidence intervals (CI) were reported for all models.

A Poisson regression model was fit to the number of tumor reports in which a recommendation was made as a function of calendar quarter with an offset for log-transformed total number of tumor reports to assess whether the number of recommendations changed over time.

All analyses were conducted using R v3.5.2 (13). *P* values less than .05 were considered statistically significant. Additional

Table 1. Baseline characteristics for the overall analytic cohort*

Characteristic	Overall (n = 164)
Female, No. (%)	109 (66.5)
Age of cancer onset, y	57 [19, 88]
Current status, No. (%)	
Alive	83 (50.6)
Deceased	69 (42.1)
Unknown	12 (7.3)
Age at tumor report, y	61.5 [19, 90]
Ethnicity, No. (%)	
Caucasian or Northern European	84 (51.2)
Asian	25 (15.2)
Ashkenazi Jewish	20 (12.2)
Hispanic	20 (12.2)
Other†	15 (9.1)
Cancer stage, No. (%)‡	
1	18 (11.2)
2	22 (13.7)
3	60 (37.3)
4	61 (37.9)
Foundation Medicine report, No. (%)	134 (81.7)
BRCA1 gene, No. (%)	83 (50.6)
Double hits in tumor sample, No. (%)	
No double hits	157 (95.7)
Two *BRCA1* variants	1 (0.6)
Two *BRCA2* variants	6 (3.7)

*Continuous and categorical variables are reported as median [range] and count (percentage), respectively.
†Includes Indian (5), African American (3), Middle Eastern (3), Native American (2), Pacific Islander (1), and unknown (1).
‡Stage at time of cancer diagnosis of the profiled tumor.

details on the statistical analysis can be found in the Supplementary Methods, available online.

Results

Cohort Characteristics

A total of 164 individuals had TS and were found to have P/LP mutations in BRCA, with the majority collected from Foundation Medicine reports (81.7%). Of these patients, 83 (50.6%) had a *BRCA1* variant by somatic TS (Table 1) and 7 (4.3%) patients were found to have two mutations within the tested specimen, in either *BRCA1* or *BRCA2*. Gynecologic cases were the most common tumor type (39%), followed by gastrointestinal (14.6%) and genitourinary (9.8%) diagnoses (Table 2).

Germline-Testing Referrals and Recommendations

Of 164 individuals found to have a P/LP *BRCA1/2* variant by TS, 113 patients (68.9%) were recommended germline testing or referred for genetic counseling (Table 3). Of the 113 patients, 87 (77%) were referred or recommended because of other clinical or histologic indications prior to the release of the TS report. Overall, 98 (59.8%) individuals had evidence of *BRCA1/2* germline testing, with 97 results available within the medical record; the results for one patient could not be identified because the patient was tested at an outside institution and there was no record of the final result in all available medical chart notes. Of the 97 patients, 54 (55.7%) tested germline positive for the same

Table 2. Breakdown of primary tumor tissue types and germline results

Tumor grouping	Overall, No. (%) (n =164)*	*BRCA1/2* Positive, No. (%) (n = 54/97)†
Gynecologic	64 (39.0)	31/57 (54.4)
Ovarian	49 (76.6)	29/46 (63.0)
Endometrial	8 (12.5)	1/5 (20.0)
Peritoneal	4 (6.3)	1/4 (25.0)
Fallopian tube	3 (4.7)	0/2 (0)
Gastrointestinal	24 (14.6)	10/16 (62.5)
Colorectal	11 (45.8)	2/6 (33.3)
Pancreatic	10 (41.7)	6/8 (75.0)
Gastric	2 (16.7)	1/1 (100.0)
Esophageal	1 (4.2)	0/1 (0)
Genitourinary	16 (9.8)	1/3 (33.3)
Prostate	9 (56.3)	0/2 (0)
Bladder	6 (37.5)	0
Kidney	1 (6.3)	1/1 (100)
Lung	15 (9.1)	1/2 (50.0)
Breast	15 (9.1)	6/14 (42.9)
Sarcoma	11 (6.7)	3/3 (100.0)*
Skin	8 (4.9)	0
Squamous cell	5 (62.5)	0
Merkel cell	2 (25.0)	0
Melanoma	1 (12.5)	0
Head and neck	5 (3.0)	1/1 (100.0)
CNS/PNS	5 (3.0)	0
Other‡	1 (0.6)	1/1 (100.0)

*For the "Overall" column, percentage within each subgroup is out of the overall group count. CNS/PNS = central nervous system or peripheral nervous system.
†A total of 97 patients had germline-testing results.
‡Includes a perivascular epithelioid cell tumor (pecoma).

Table 3. Clinical action based on tumor report*

Report results	Overall, No. (%)† (n = 164)
Referral or recommendation	113 (68.9)
Referral timing	
Before tumor sequencing	87 (77.0)
After tumor sequencing	26 (23.0)
Evidence of genetic counseling visit	80 (48.8)
Genetic counseling location	
Stanford	67 (83.8)
Outside of Stanford	13 (16.2)
Germline testing performed	98 (59.8)
Germline-testing result*	
BRCA1/2 positive	54 (55.7)
BRCA1/2 negative	43 (44.3)
Germline-testing location	
Tested at Stanford	63 (64.3)
Tested outside of Stanford	35 (35.7)
Tumor report date after publication of NCCN guidelines	108 (65.9)

*Categorical variables are reported as count (percentage). NCCN = National Comprehensive Cancer Network.
†Of the patients who had germline testing, the results for one patient could not be identified because the patient was tested outside the institution and there was no record of the results in the notes available.

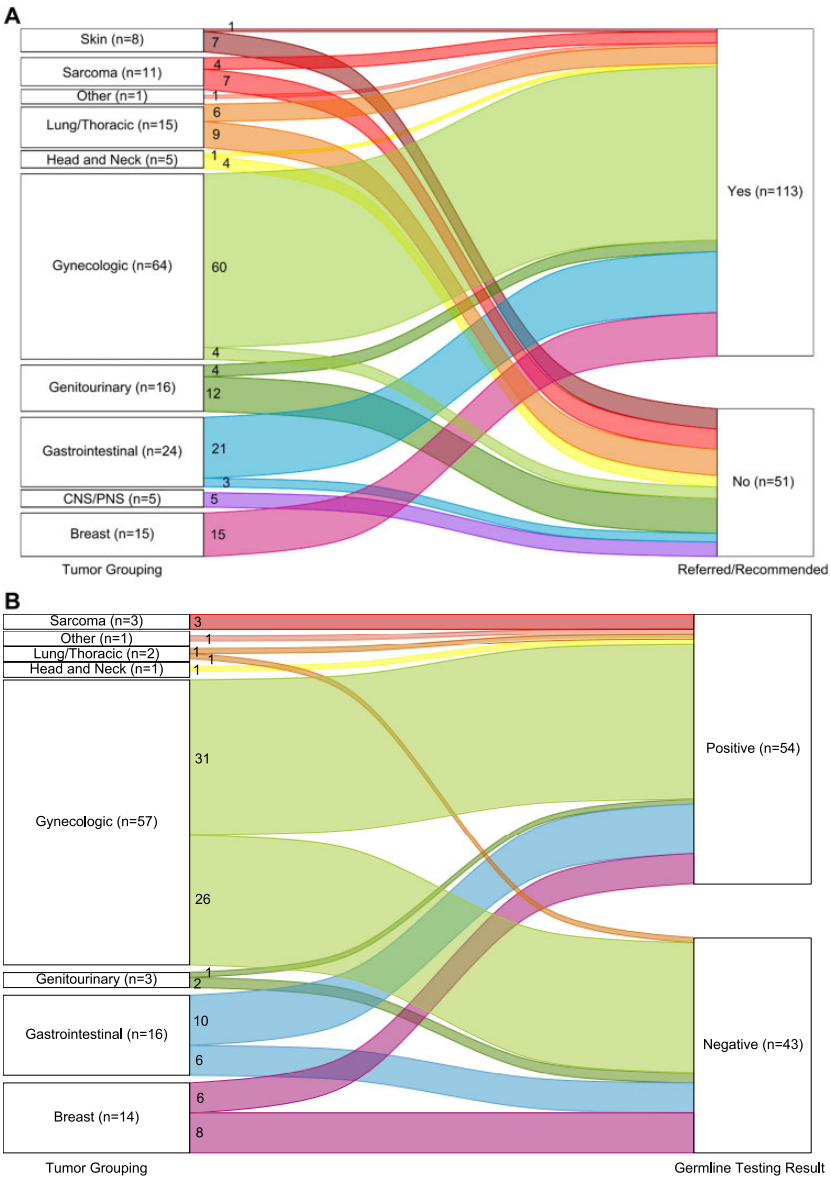

Figure 1. Sankey Diagrams. **A)** Sankey diagram of tumor grouping by referral status. Visualization of germline testing referrals or recommendations by tumor grouping. Counts next to each tumor grouping denotes the number of patients in that path. **B)** Sankey diagram of tumor group by germline testing result. Visualization of germline testing results by tumor grouping for patients who were recommended or referred for testing. Counts next to each tumor grouping denote the number of patients in that path. CNS/PNS = central nervous system/peripheral nervous system.

BRCA1/2 variant on the TS report. Of those referred or recommended germline testing, the majority (66.4%) had a breast or gynecologic cancer, and all 15 breast cancer cases were recommended germline testing (Figure 1A). Supplementary Table S1 (available online) further describes referrals or recommendations for germline testing by tumor group, and Figure 1B depicts germline-testing results by tumor group.

Which Factors Influenced a Referral or Recommendation for Germline Testing?

Sex ($P < .001$), age of cancer onset ($P = .003$), age at time of tumor report ($P = .002$), cancer stage ($P = .02$), and VAF ($P < .001$) were bivariately associated with whether a patient was referred or recommended for germline testing (Table 4). Adjusting for possible confounders, the aforementioned factors were no longer statistically significantly associated with whether a patient was referred or recommended for germline testing, excluding age of cancer onset (OR = 0.95, 95% CI = 0.90 to 0.99; $P = .032$). Our analysis also found that patients with genitourinary cancer (OR = 0.03, 95% CI = 0.00 to 0.26; $P = .002$), lung cancer (OR = 0.04, 95% CI = 0.01 to 0.21; $P < .001$), sarcoma (OR = 0.02, 95% CI = 0.00 to 0.15; $P < .001$), skin cancer (OR = 0.01, 95% CI = 0.00 to 0.16; $P = .002$), or "other" diagnoses (OR = 0.01, 95% CI = 0.00 to 0.12; $P < .001$) were statistically significantly less likely to be referred or recommended germline testing compared with patients with breast or gynecological diagnoses (Figure 2).

Table 4. Baseline characteristics by referral or recommendation*

Characteristic	Referred or Recommended for Germline Testing		
	No (n = 51)	Yes (n = 113)	P
Sex, No. (%)			
Male	32 (62.7)	23 (20.4)	<.001
Female	19 (37.3)	90 (79.6)	
Age of cancer onset, y	61 (24, 85)	54 (19, 88)	.003
Age at tumor report, y	69 (30, 87)	58 (19, 90)	.002
Ethnicity, No. (%)			
Caucasian or Northern European	32 (38.1)	52 (61.9)	.30
Asian	6 (24.0)	19 (76.0)	
Ashkenazi Jewish	3 (15.0)	17 (85.0)	
Hispanic	6 (30.0)	14 (70.0)	
Other†	4 (26.7)	11 (73.3)	
Cancer stage, No. (%)‡			
1	9 (50.0)	9 (50.0)	.022
2	5 (22.7)	17 (77.3)	
3	11 (18.3)	49 (81.7)	
4	23 (37.7)	38 (62.3)	
Variant allele frequency (VAF)	33 [1, 90]	50 [1, 91]	<.001
VAF 30%+, No. (%)	24 (24.0)	76 (76.0)	.03
Tumor report date after publication of NCCN guidelines, No. (%)			
No	19 (37.3)	37 (32.7)	.70
Yes	32 (62.7)	76 (67.3)	

*Differences in continuous variables by referral status were tested using the Wilcoxon rank sum test. Differences in categorical variables by referral status were tested using the χ^2 test except for Ethnicity, for which Fisher exact test was used. Percentages for ethnicity are reported within each row. All other percentages are out of column totals. NCCN = National Comprehensive Cancer Network.

†Includes Native American, Pacific Islander, African American, Indian, and Middle Eastern.

‡Stage at time of cancer diagnosis of the profiled tumor.

Variant Allele Frequency and Germline-Testing Results

Although VAF was not found to be associated with germline-testing recommendations, a higher VAF was found to be statistically significantly associated with positive germline-testing results in the bivariate and multivariable setting (adjusted OR = 1.06, 95% CI = 1.03 to 1.10; $P < .001$) (Figure 3; Supplementary Table S2, available online). A VAF threshold of 47% was found to accurately distinguish between positive and negative germline-testing results with moderate area under the curve (AUC = 0.79, 95% CI = 0.61 to 0.94) and accuracy (0.76, 95% CI = 0.64 to 0.88).

Referrals or Recommendations Over Time

In documenting the date of each tumor report, it was observed that 56 (34.1%) reports were released before the publication of the NCCN practice guideline (Table 3). Referrals or recommendations did not statistically significantly change over time for the entire cohort (risk ratio [RR] = 1.02, 95% CI = 0.90 to 1.16; $P = .8$; Supplementary Figure S1, available online) or among non-breast and/or ovarian tumor types (RR = 0.99, 95% CI = 0.80 to 1.27; $P = .96$; model not shown). Further, there were no statistically significant differences in referral or recommendation patterns before or after the September 19, 2016, NCCN guideline publication (OR = 2.05, 95% CI = 0.65 to 6.79; $P = .22$; Figure 2).

Discussion

Somatic TS is an integral diagnostic tool used to aid in targeted treatment decisions and to indicate clinical trial eligibility. Without matched tumor-normal sequencing, the ability to definitively separate somatic and germline changes remains a challenge. NCCN guidelines state that any P/LP *BRCA1/2* mutation identified by tumor-only sequencing meets criteria for germline testing, regardless of tumor type. Our study highlights a disparity in recommendation rates at our institution for germline testing based on somatic *BRCA1/2* findings. Almost one-third (31.1%) of participants within our cohort were not referred for genetic counseling or recommended germline testing. Many of these patients had genitourinary, lung, sarcoma, skin, or other cancer diagnoses, which were statistically significantly less likely to be recommended germline testing in comparison with gynecologic or breast cancer diagnoses. Confirmation of a germline *BRCA1/2* mutation allows an individual to be informed of future cancer risks and counseled appropriately on screening or prophylactic surgery options, and it provides the opportunity to notify relatives who may benefit from testing as well.

The differences in recommendation rates between tumor groups could be influenced by our clinical understanding of *BRCA1/2* and their subsequent cancer risks. Because these genes are most often associated with breast and ovarian cancer, oncologists who practice within either specialty may be more familiar with hereditary predispositions, such as HBOC syndrome. Given that all breast cancer cases and 95.9% of ovarian cancer cases were recommended germline testing (Supplementary Table S1, available online), provider awareness of HBOC syndrome is evident and their practice of referral is in accordance with national standards. This is not surprising because patients with breast or ovarian cancer are often referred for genetic counseling because of additional, preexisting NCCN guidelines. For instance, all women who have a personal history of ovarian cancer have met criteria for germline *BRCA1/2* testing since 2007 based on national guidelines, and certain histological markers or a strong family history of cancer may render a patient with breast cancer eligible for germline testing (14). These guidelines, which predate the 2016 NCCN statement pertaining to *BRCA1/2* findings on TS, likely explain why such a substantial proportion of our cohort were recommended germline testing prior to undergoing TS.

In contrast, providers in other specialties outside of breast and gynecology may not recognize the role of *BRCA1/2* in cancer risk, even when a pathogenic variant is identified within a patient's tumor. In fact, the tumor groups less likely to be recommended germline testing by our analysis (lung, skin, sarcoma, genitourinary, and "other" diagnoses) are those not typically associated with hereditary cancer syndromes, let alone *BRCA1/2* variants. In support of this idea, although colorectal cancer is not typically associated with germline *BRCA1/2* variants, it is highly associated with Lynch syndrome, and 90.9% of these patients were recommended germline testing (Table 4), suggesting physician awareness of hereditary cancer syndromes. It is worth keeping in mind, however, that although oncologists at our institution and similar tertiary centers may be specialized to treat specific primary tumor types, this is not always the case in the broader community of providers that routinely order somatic tumor sequencing. Nevertheless, the data demonstrate that particular diagnoses at our institution are less likely to be recommended germline testing, despite that the national guideline apply to all tumor types. Regardless of the primary diagnosis, carriers of germline *BRCA1/2* mutations will have a high risk

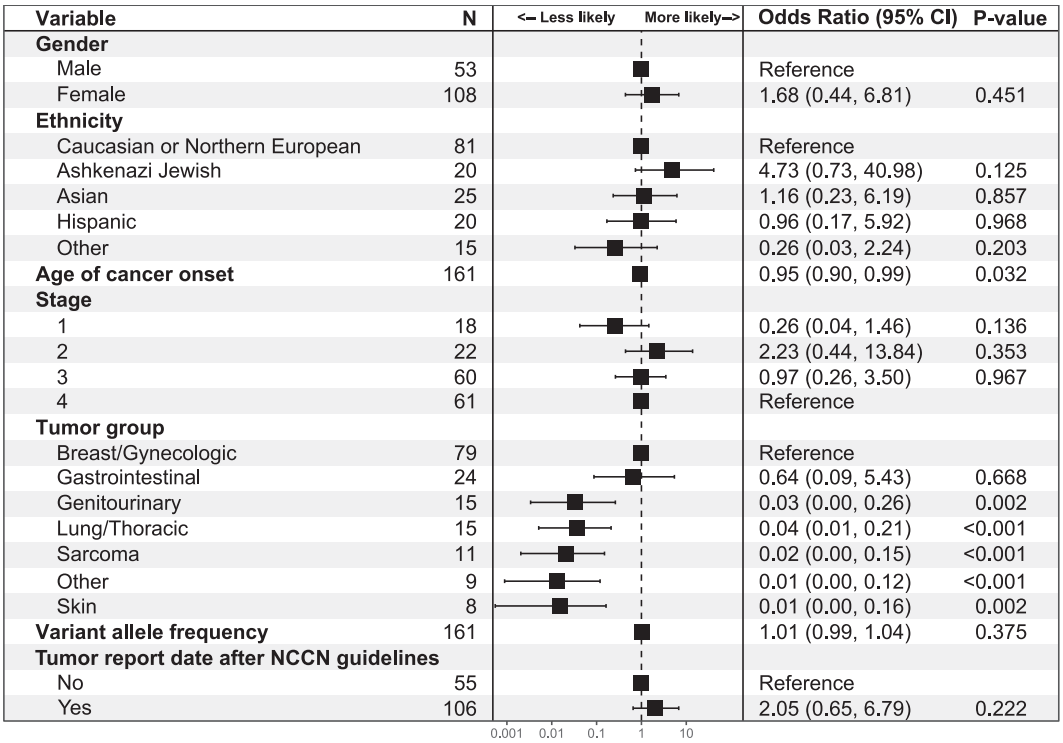

Figure 2. Forest plot of odds of germline testing referral or recommendation. Forest plot reporting odds ratios from multivariable logistic regression model fit to whether or not a patient was referred or recommended for germline testing as a function of all variables reported above. "Other" tumor group includes a perivascular epithelioid cell tumor (pecoma), head and neck, and central nervous system/peripheral nervous system. Results from the Hosmer-Lemeshow goodness-of-fit test suggested the model fit was appropriate ($\chi^2 = 5.22$, $P = .73$). NCCN = National Comprehensive Cancer Network.

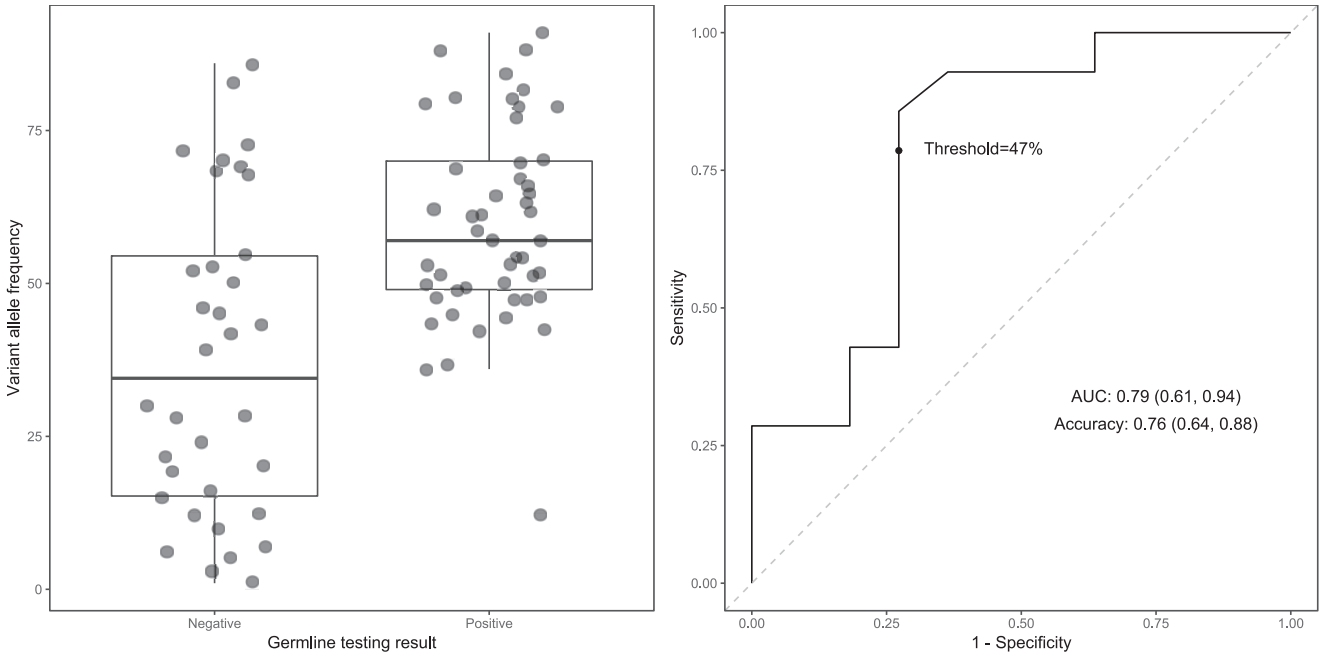

Figure 3. Variant allele frequency (VAF) by germline testing result. Summary of VAF and germline testing result analysis (n = 83 with nonmissing VAF and germline testing results). **A)** Displays boxplots of variant allele frequency by whether the germline-testing result was positive or negative. **B)** Displays the receiver operating characteristic curve analysis of germline-testing result and VAF applied to the 40% heldout test data (n = 25). At a threshold of 47% for VAF, the optimal sensitivity and specificity were 0.79 and 0.73, respectively. Area under the curve (AUC) and accuracy were similar between the training and test sets. The **dashed diagonal line** represents a test that does not distinguish at all between positive and negative germline results.

for breast and ovarian cancer. Recommendation rates do not appear to have changed since the initiation of the NCCN guideline in 2016 either, indicating there may be a lack of familiarity around standard TS protocol and the potential for germline variants (Supplementary Figure S1, available online).

In addition to tumor type, age of cancer onset was also found to be a statistically significant indicator for germline referral (Figure 2). Whereas a younger cancer onset may increase suspicion of an underlying hereditary cancer syndrome, we found minimal clinical difference in the average age of onset of those recommended germline testing (54 years) and those who were not (61 years). In fact, when all breast and gynecologic cases are removed from analysis (Supplementary Figure S2, available online), age of cancer onset is no longer statistically significant (OR = 0.94, 95% CI = 0.99 to 1.00; $P = .052$). This is likely because breast and ovarian cancers tend to be diagnosed on average at younger ages than other cancer types, such as lung or colorectal cancer (15).

VAF was not found to be statistically significantly associated with germline-testing recommendations. The Stanford Tumor Actionable Mutation Panel specifies the VAF of tumor variants on the report that is ultimately given to the ordering provider, but VAF is not routinely provided on FM reports. Most of the participants within our cohort had FM testing, which could explain why VAF was not statistically significantly associated with germline-testing recommendation rates. Although VAF was not associated with germline-testing recommendations, it was found to be statistically significantly associated with positive germline *BRCA1/2* results (Figure 3). Figure 3 illustrates that a VAF threshold of 47% has adequate ability to discriminate positive and negative germline-testing results. This is in line with the Association for Molecular Pathology, the American Society of Clinical Oncology, and the College of American Pathologists joint consensus: Alleles identified by TS at a frequency between 0.5 and 1.0 are more likely to be true germline results (10).

One limitation of this study was the reliance on documentation within the medical record. It is possible that patients had conversations with medical providers about germline testing that were subsequently not recorded within clinical notes. We had also intended to assess whether patients who were recommended germline testing had family histories of cancer that met germline-testing criteria. Documentation of family history varies markedly within the medical record, and we found that patients who had seen a genetic counselor were more likely to have a family history of cancer that met NCCN criteria for germline testing. This was often because genetic counselors take three-generation pedigrees, whereas other providers may not ask for detailed family history information.

Considerations for incidental germline findings will continue to persist as tumor-only sequencing becomes more routine and as matched tumor-normal testing remains a challenge for institutions to launch. Provider education and awareness around germline implications, especially for those practicing outside of breast and gynecology, is needed to increase referrals to genetic counseling and germline testing for patients with somatic *BRCA1/2* variants. Even though most cancer is not directly caused by a hereditary predisposition, oncologists who order TS should be educated on national standards for recognizing potential germline risks associated with TS results. The substantial yield of germline *BRCA1/2* mutations, and the impact that mutations have on patients and their families, prompted the NCCN to publish the statement in the first place. For there to be a subset of patients not recommended germline testing as an option represents a gap in clinical care at our institution. It is worth keeping in mind that there are additional genes consistently included on commercially ordered somatic panels that are associated with other, distinct hereditary cancer syndromes beside HBOC syndrome. Even so, there are currently no comparable NCCN guidelines for genes relevant to other inherited cancer predispositions, such as Lynch syndrome, that outline how to best address potential germline findings that may arise as a result of TS. However, research is beginning to support recommendations for germline follow-up testing, including a recent study from the European Society of Medical Oncology's Precision Medicine Working Group (16). Further investigation is warranted into additional genes with germline implications to inform us on how to best care for and consent our patients that are undergoing TS.

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Notes

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