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Breadth of genetic testing selected by patients at risk of hereditary breast and ovarian cancer

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Abstract

Objective—To evaluate the ability of patients at risk of hereditary breast and ovarian cancer (HBOC) syndrome to select the extent of genetic testing personally preferred and the impact of demographic factors on the breadth of testing pursued.

Methods—A single-institution cohort was enumerated consisting of patients referred for clinical genetic counseling (CGC) secondary to risk of HBOC syndrome. This was a retrospective study of consecutive patients seen for genetic counseling; all patients completed an epidemiologic questionnaire and provided personal and family medical histories. Patients meeting guidelines for testing were offered testing at three levels: single gene/condition (Single), small panels with highly penetrant genes (Plus), and large panels with high and moderately penetrant genes (Next). Associations between personal or family related factors and breadth of testing selected were investigated. Continuous and categorical variables were compared using Student's *t* and χ^2 tests, as appropriate. Joint classification tables were used to test for effect modification and a log-binomial model was used to compute rate ratios (RR) with a threshold of $p < 0.05$ considered significant.

Results—We identified 253 patients who underwent genetic counseling for HBOC syndrome. Most patients were personally affected by cancer (63.6%), reported at least some college (79.2%), met NCCN guidelines for BRCA testing (94.5%), and opted to undergo genetic testing (94.1%). Most (84.9%) patients opted for panel testing. An increased likelihood of choosing Next-level testing was found to be associated with patients having any college experience (RR: 1.53, 95%CI: 1.02-2.30), as well as being unaffected by cancer (RR: 1.30, 95%CI: 1.03-1.64).

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Conclusion—CGC is a highly specialized service, which should be provided to patients at risk of hereditary cancer syndromes. Although some epidemiologic factors can predict a patient's preference for testing breadth, patients were sufficiently able to self-identify the level of testing they were comfortable with after receiving genetic counseling. Most practitioners do not have the time or expertise to provide the degree of counseling needed to enable and empower patients to choose the level of testing they are comfortable with. When available, referral to genetic counselors remains an important component of comprehensive care for women with a personal or family history of cancer suggestive of hereditary risk.

Introduction

The hereditary breast and ovarian cancer syndrome (HBOC) has been clinically recognized since the early 1970s and the discovery of the BRCA1 and BRCA2 genes in 1990 and 1994, respectively, provided a scientific basis for testing affected patients and their unaffected family members for mutations (1, 2). Since 2013 the availability of multigene panel tests has become more widespread (1, 3), the breadth of which includes well understood, highly penetrant genes that confer a high risk of cancer, as well genes in which the risk of breast and or ovarian cancer is less well defined (3, 4).

Multiple organizations including professional societies and the Centers for Disease Control (CDC) have published recommendations for identifying patients at risk for BRCA mutations (5-10). Despite recognition of the importance of BRCA testing, few recommendations exist regarding testing of other genes associated with increased cancer risk in the HBOC spectrum. A remaining question is what is the appropriate breadth of testing for patients at risk of HBOC?

In the absence of guidelines, decision making about testing remains individualized based on characteristics of the patient and the counseling practitioner. This study aimed to determine a patient's ability to self-identify the extent of genetic testing personally desired, as well as determine if epidemiologic factors may predict the breadth of genetic testing a patient selects. We hypothesized that in response to standardized counseling a combination of personal and family related characteristics is associated with breadth of requested testing. We tested this hypothesis through a cohort study enrolling patients referred for genetic counseling and monitoring the breadth of testing pursued.

Materials and Methods

Study design and patient selection

This was an IRB-approved retrospective cohort analysis of patients seen for consultation by certified genetic counselors at our institution from 1/1/2015 to 9/30/2015. Prior to consultation, patients completed an intake form that elicited demographic information and personal and family medical histories. Patients were included if they were referred as new patients for genetic consultation during the study accrual period. They were excluded if there was a known mutation in the family, if they had received genetic testing prior to referral, if they were referred for non-HBOC related histories, if their insurance did not approve testing through Ambry Genetics (Aliso Viejo, CA), or if they declined genetic testing.

As part of their counseling, patients received standardized, non-directive counseling, with respect to the breadth of genetic testing available. Specific attention was paid to the number of genes that were not currently clinically actionable, and the potential for a higher rate of variants of unknown significance. All testing was performed through Ambry Genetics and patients opting to undergo testing were scheduled for result disclosure to be performed in person or by phone. The primary outcome was breadth of testing ordered: Single gene/condition testing, which tests for mutations in the BRCA1 and BRCA2 genes alone; “Plus” level testing, which also tests for other highly penetrant genes associated with breast and/or ovarian cancers (in addition to BRCA1 and BRCA2); and “Next” level testing, which includes the analysis of moderately penetrant genes (i.e. those with uncertain impact on cancer risk) in addition to the genes on the “Plus” panel. Patients selecting reflex-testing, in which a limited test was initially performed and then a larger panel would be performed if the initial test results were negative, were categorized according to the maximum level of testing planned. The genes included in each level of testing are listed in Table 1. There is presently no difference in out of pocket cost of the test to patients with insurance coverage (either commercial or government) as there is limited reimbursement for multigene panels. The results of genetic testing were recorded as a secondary outcome. Predictor variables include age at the time of counseling, educational attainment recorded on the patient intake form, and personal and familial cancer histories as elicited during the clinical encounter. Counseling setting (individual, family, or group) and the individual counselor were evaluated as potential effect modifiers. Additionally, reported ethnic background, as well as satisfaction of 2015 NCCN guidelines for testing of various cancer syndromes (i.e. Li-Fraumeni, Lynch, and Cowden syndromes) were considered possible confounders.

To avoid interviewer bias the counselors agreed upon a standard set of communication objectives to include in their counseling. However, there was not a single standardized script, so it is possible that differences in delivery of the counseling message could have been present. Because patients were counseled and made decisions during the same clinic visit, loss to follow up bias is non-existent in this cohort. Finally, it is possible that patients who follow-through for genetic counseling are fundamentally different from those who are referred but never seen for counseling or testing. This distinction is important for healthcare providers in the clinical setting and it may restrict the generalizability of this study to those patients who receive genetic counseling, rather than those who are simply referred.

Statistical Analysis

Due to the exploratory nature of this study, the sample size was determined according to the number of eligible patients who were seen in clinic during the enrollment period. The breadth of testing was categorized according to number and penetrance of genes tested in the panel. These classifications were made according to the nomenclature used by the testing laboratory. BRCAplus and GYNplus were the “Plus” level tests, while BreastNext, OvaNext, PancNext, and CancerNext were the “Next” level tests. Genetic results were classified as normal, variant of unknown significance (VUS), or pathogenic; additionally, notation was made according to the minimum testing breadth required to identify the mutation. With respect to coding of variables: age was parsed into decades; educational attainment was dichotomized according to any or no college attendance; a dichotomous variable for whether

or not the patient was personally afflicted with cancer was created, as well as individual variables for breast, ovarian, colon, and other cancers; family history was quantified as positive or negative for maternal and paternal lineages, as well as degree of relation (first-, second-, or third-degree).

Continuous and categorical variables were compared using Student's t and χ^2 tests as appropriate with a threshold of $p < 0.05$ considered significant. Joint classification tables were used to test for effect modification and a log-binomial was used to compute crude and adjusted rate ratios (RR, aRR). The log-binomial model was selected over the more common logistic model due to the relative frequency of panel testing in this cohort (11). Standard model diagnostics were performed to confirm convergence of the model. Patients with missing data with respect to exposure variables were excluded from analysis in which those exposure variables were assessed. Those with missing primary or secondary outcome variables were excluded from analysis. A sensitivity analysis was performed to determine the appropriate categorization of educational attainment. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

There were 384 patients seen for initial counseling with the genetic counselors between January 1, 2015 and September 30, 2015. We excluded 52 who had prior testing in the community before being counseled by our genetics service, 41 with a known familial mutation, 34 referred for non-HBOC indications and three patients whose insurance did not allow testing through Ambry Genetics; this left 253 patients available for analysis. The descriptive characteristics of patients included in the study are presented in Table 2. The average age of patients being counseled was 53 years (range 23 to 87 years). Most patients were personally affected by cancer (63.6%), reported at least some college (79.2%), and opted to undergo genetic testing (94.1%). With respect to family history of cancer, most patients had affected relatives in their nuclear (80.9%), second-degree (90.8%), and/or third-degree (68.7%) families; only 11 (4.4%) patients reported Ashkenazi Jewish ancestry. Most (94.5%) of the patients referred for testing with suspected susceptibility to HBOC syndrome met NCCN guidelines for BRCA1/2 testing; additionally, 4.7% of patients qualified for TP53 gene testing, 3.2% for PTEN gene testing, and 7.5% for Lynch syndrome testing. After excluding the 15 patients who did not elect to undergo testing, 238 patients were included in the final analysis.

Thirty-six patients (15.1%) declined panel testing and had only testing for BRCA1 and BRCA2 with two mutations and four VUSs identified. Of the patients who selected panel testing, 76 desired Plus-level testing while 126 had Next-level testing ordered. There were five mutations and 10 VUSs identified in the Plus-level tests, including three BRCA mutations. The Next-level tests identified 12 mutations (two BRCA mutations) and 35 VUSs. In total: five BRCA1 mutations were identified; three monoallelic MUTYH mutations; two mutations each in BRCA2, CHEK2, PALB2, and TP53; as well single APC, BRIP1, and MSH2 mutations.

Attendance at college was associated with breadth of testing ($p = 0.011$), with those reporting any college experience being 53% more likely to choose Next-level testing than those without college experience (RR: 1.53, 95% CI: 1.02-2.30). Patients who were not affected by cancer were more likely to request Next-level testing ($p = 0.039$). Breast cancer diagnosis was not associated with breadth of testing ($p = 0.859$), while ovarian cancer diagnosis was associated with testing breadth ($p = 0.027$); specifically they were more likely to select Next-level testing. Patients whose siblings were affected with cancer were significantly more likely to order Next-level testing ($p = 0.005$), but neither having affected children nor parents was associated with breadth of testing ($p = 0.508$ and $p = 0.878$, respectively). Age and familial cancer history outside of the patient's nuclear family were also not associated with breadth of testing. We investigated both the degree of closest relation with cancer and whether the cancer history comes from the maternal or paternal lineage and in neither case was history predictive of testing breadth ($p > 0.10$). Although the counseling setting (individual vs. group consultation) was not associated with breadth of testing, the distribution of testing breadth according to genetic counselor was not evenly distributed ($p = 0.045$); however, the distribution of Ashkenazi Jewish ancestry was not evenly distributed between counselors and after adjusting for reported heritage the differences in breadth according to counselor were no longer significant ($p = 0.747$).

We investigated the association between the significant predictors above and specific breadth of testing and found that the associations were driven by selections for Next-level testing. Therefore, for the remainder of calculations we report associations with Next-level testing. The impact of a patient's personal cancer history on the association between college experience and breadth of testing is presented in Table 3. Patients who were personally affected with cancer and attended college had a two-fold increased rate of selecting a Next-level test (RR: 2.03, 95% CI: 1.25-4.78); the association was opposite that observed in unaffected patients, where college educated non-affected patients were 20% less likely to request Next-level testing; however this association was not statistically significantly different (RR: 0.80, 95% CI: 0.55-1.18).

Breadth of test was also associated with the number of familial cancer syndromes for which a patient satisfied testing requirements. Specifically, there were associations between breadth and meeting criteria for Lynch or HBOC syndromes ($p = 0.037$ and $p = 0.031$, respectively), but not Cowden or Li-Fraumeni ($p > 0.30$). If patients met criteria for multiple familial cancer syndromes they were more likely to have at least Plus-level testing ($p = 0.012$) compared with those who only met criteria for one familial cancer syndrome. Therefore, we sought to evaluate the effect of college experience and personal cancer history on patients who only qualified for genetic testing for HBOC syndrome. Among those patients, college experience was still associated with a 58% increased rate of selecting a Next-level test (aRR: 1.58, 95% CI: 1.003-2.50). Having the closest affected family member be part of the nuclear family was still associated with Next-level testing ($p = 0.003$). Neither sidedness of qualification for testing (maternal vs. paternal) nor age at the time of counseling was associated with breadth of testing, even after restricting for HBOC patients only.

Discussion

In this cohort of patients referred for initial genetic counseling due to elevated risk of HBOC syndrome, breadth of genetic testing selected was associated with education level and personal cancer history. Personal cancer history had a differential effect on breadth of testing requested according to whether or not a person had any college experience. These results remained significant even after restriction to patients who were appropriate candidates for HBOC testing but not any other familial cancer syndromes based on current NCCN criteria. The frequency of non-BRCA mutations in this cohort was 3.8% for Plus-level tests and 7.9% of Next-level tests, consistent with prior reports of expanded genetic testing (4, 12). VUSs were also identified at each level of testing, with more than a quarter (27.8%) of patients undergoing Next-level testing having an indeterminate result.

This study population was limited to patients who underwent clinical genetic counseling. We did not address any potential differences between the counseled patients and those who were not referred or referred but did not follow-through with scheduled appointments. The standard workflow at our institution is that patients are offered referral for clinical genetics evaluation by their treating physicians, and genetic testing is ordered through the clinical genetics service only. A prior study at another cancer center identified referral rates of 34% and 14.5% for breast and ovarian cancer patients meeting NCCN criteria, respectively (13). Although age and family history were identified as significant risk factors for referral in that study, they were not associated with breadth of testing in the present study. The sample population of the present study is from a regional cancer center, which may not be representative of the general population; a recent publication reported only 36.8% of patients – only 12.3% of patients seen by obstetrician/gynecologists – undergoing BRCA testing received genetic counseling from a clinical genetics provider(14).

This study also did not directly query patients about their reasons for pursuing genetic counseling or testing, or for selecting one level of testing over another. Other studies have investigated women's reasons for following through with counseling or testing and have identified concern about ovarian cancer risk, support from their primary care physician, and recommendation from a primary physician(15-19). We counseled patients about the risk of and uncertainty with VUS results with larger panels and this was borne out in the data with a 31% VUS rate in the largest panel. Counseling emphasized both before and after testing that the uncertainty with VUS may never be resolved. The uncertainty of VUS along with other risks and benefits of testing are summarized in Table 4.

The downstream impact, both psychologically and financially, to both the patient and the health care system related to an un-actionable result from genetic testing can be minimized when appropriate pre- and post-test counseling is provided. As there may be some psychological distress with regard to receiving a result with an uncertain clinical significance (either a VUS or a positive result in a gene with limited information), discussion regarding this possibility is a focus of the pre-test counseling, in an effort to minimize psychological distress in patients. Minimally, pre-test counseling should include a discussion of the different testing options available, that the genes tested confer different lifetime cancer risks, unclear knowledge of such risk for some genes, and the likelihood of receiving an

uncertain result, which varies with testing breadth. Review of a patient's attitude toward risk and their emotional ability to handle receiving inconclusive results should be assessed to assist the patient in determining their own optimal level of testing. Anecdotally, psychological distress seemed to be limited as patients were informed during pre-test counseling of their testing options (and the pros and cons of each) and empowered to self-select their extent of testing, as well as provided with adequate post-test counseling to review the interpretation and significance of an uncertain result for them and their family. Further, financial burden to the health care system is minimized when patients receive post-test counseling by a formally trained genetics provider to ensure that appropriate medical management recommendations are made based on the genetic test result, and that patients are not receiving unnecessary screenings or interventions based on an uncertain result.

The paradigm of genetic testing has seen a rapid change with the introduction of multigene panel testing; however, consensus guidelines suggesting which patients should be offered what degree of testing do not exist. Genetics providers must balance the potential of identifying a mutation imparting indeterminate cancer risk, which may increase patient confusion and anxiety, with the possibility of missing a gene that could classify a family as having increased risk and prompt enhanced cancer screening. This study supported the idea that patients receiving comprehensive, non-directional genetic counseling are able to self-identify the extent of genetic testing with which they are comfortable. This comfort should include an understanding and acceptance of the uncertainty that can arise from results obtained in larger panels, where a mutation may be identified but without clear-cut recommendations for prevention, screening, or treatment. Additionally, this study also identified multiple epidemiologic associations with patients' self-identified preferences for breadth of genetic testing; further underscoring the need for comprehensive genetic counseling. Because most clinicians do not have the time or expertise to counsel patients through these various decision processes, it is important to continue to involve clinical genetic counselors in patient care discussions and the genetic testing process. Further studies are needed to not only confirm these findings, but additionally to investigate the role of other factors, such as personality traits/characteristics, on patient decision making.

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Table 1

Evidence Level	Single-Gene Testing	Plus-level Testing	Next-level Testing
Established and recognized guidelines	BRCA1, BRCA2	BRCA1, BRCA2, CDH1, EPCAM, MLH1, MSH2, MSH6, PMS2, PTEN, TP53	BRCA1, BRCA2, CDH1, STK11, PTEN, TP53, MLH1, MSH2, MSH6, PMS2, EPCAM, APC, BMPR1A, SMAD4, NF1, MUTYH (homozygote)
Limited guidelines			ATM, CDKN2A, CHEK2, PALB2
No national guidelines			BARD1, BRIP1, MRE11A, NBN, RAD50, RAD51C, RAD51D, MUTYH (heterozygote), SMARCA4, CDK4, GREM1, POLD1, POLE
Quoted incidence of VUS results [*]	3.8%	3.41% - 11.39%	21.5% - 27.68%

Level of guidelines for actionability of genes included at various breadths of panel testing (per NCCN 2015).

^{*} Quoted VUS rates from Ambry Genetics in 2015 (Plus-level range includes data for BRCAplus and GYNplus panels; Next-level includes data for BreastNext, OvaNext, and CancerNext panels)

Table 2

Demographic	Single N = 36	Plus N = 76	Next N = 126	* p
Age (years)	< 30	1(11.11)	6(66.67)	0.374
	30-39	2(6.9)	10(34.48)	
	40-49	10(19.23)	32(61.54)	
	50-59	11(13.75)	39(48.75)	
	60-69	8(15.38)	23(44.23)	
	70-79	2(16.67)	8(66.67)	
Education	80	1(25)	2(50)	0.139
	Some High School	0(0)	1(50)	
	High School Graduate	5(12.2)	21(51.22)	
	Some College	7(14.89)	10(21.28)	
	College Graduate	12(15.38)	20(25.64)	
Jewish Ancestry	Graduate/Professional	9(16.67)	19(35.19)	0.095
	No	32(14.22)	73(32.44)	
	Yes	4(40)	3(30)	
Personally Affected	Unsure	0(0)	0(0)	0.039
	No	13(16.25)	17(21.25)	
Breast Cancer	Yes	23(14.56)	59(37.34)	0.859
	No	19(14.07)	43(31.85)	
Ovarian Cancer	Yes	17(16.5)	33(32.04)	0.027
	No	30(15.38)	55(28.21)	
Family members with Cancer: Children	Yes	6(13.95)	21(48.84)	0.508
	No	29(15.59)	58(31.18)	
Siblings	Yes	2(15.38)	6(46.15)	0.005
	No	25(17.24)	54(37.24)	
	Yes	8(9.88)	18(22.22)	

Demographic		Single N = 36	Plus N = 76	Next N = 126	p *
Parents	No	8(12.31)	22(33.85)	35(53.85)	0.878
	Yes	25(14.79)	54(31.95)	90(53.25)	
2° Relative	No	3(13.64)	10(45.45)	9(40.91)	0.373
	Yes	30(14.15)	66(31.13)	116(54.72)	
3° Relative	No	12(16.44)	29(39.73)	32(43.84)	0.139
	Yes	21(13.04)	47(29.19)	93(57.76)	
Counseling Setting	Individual	27(13.99)	62(32.12)	104(53.89)	0.780
	Family	5(17.24)	10(34.48)	14(48.28)	
	Group	4(25)	4(25)	8(50)	
NCCN Qualification					
HBOC	No	2(33.33)	4(66.67)	0(0)	0.031
	Yes	34(14.66)	72(31.03)	126(54.31)	
Li-Fraumeni	No	36(15.93)	71(31.42)	119(52.65)	0.308
	Yes	0(0)	5(41.67)	7(58.33)	
Cowden	No	36(15.65)	72(31.3)	122(53.04)	0.348
	Yes	0(0)	4(50)	4(50)	
Lynch	No	36(16.36)	66(30)	118(53.64)	0.037
	Yes	0(0)	10(55.56)	8(44.44)	
Multiple	No	36(17.65)	60(29.41)	108(52.94)	0.012
	Yes	0(0)	16(47.06)	18(52.94)	

N, total number of patients receiving level of testing; n, number of patients with specific demographic; (%), percent of patients with (or without) specific demographic at each level of testing; Single, testing for BRCA1 and BRCA2 only; Plus, small panels with highly penetrant genes; Next, large panels with high and moderately penetrant genes;

2° Relative, second-degree relative such as grandparents or aunts/uncles;

3° Relative, third-degree relative such as a cousin Data are n(%). The percentages are computed from row totals.

* Testing levels compared using χ^2 .

Table 3

Cancer Type	Affected?	College?	Next-Level*	RR [†]	aRR [‡]
Any Cancer	Yes	Yes	64(55.17)	2.03(1.25-4.78)	2.51(1.28-4.91)
		No	7(22.58)		
	No	Yes	38(60.32)	0.80(0.55-1.18)	0.83(0.57-1.22)
		No	9(75.00)		
Breast	Yes	Yes	44(55.70)	1.81(0.78-4.19)	1.88(0.81-4.35)
		No	4(30.77)		
	No	Yes	58(58.00)	1.45(0.91-2.32)	1.48(0.93-2.36)
		No	12(40.00)		
Ovarian	Yes	Yes	13(52.00)	3.12(1.04-9.37)	3.12(1.04-9.37)
		No	3(16.67)		
	No	Yes	89(57.79)	1.11(0.74-1.66)	1.15(0.77-1.71)
		No	13(52.00)		

Affected, whether the patient was affected with the given cancer; College, whether the patient reported any college education on their epidemiologic questionnaire; Next-Level, large panels with high and moderately penetrant genes; RR, rate ratio; aRR, adjusted rate ratio

*Data are reported n(%) for those selecting Next-level testing

[†]Data are reported RR(95% confidence interval). The numbers of events are provided in the "Next-Level" column

[‡]Data are reported RR(95% confidence interval). The numbers of events are provided in the "Next-Level" column. The multivariate model included qualification for national testing guidelines.

Table 4

	Single-gene	Plus-level Testing	Next-level Testing
Risks/ Burden to patient	Only testing for a single condition; can miss identification of hereditary condition in family if testing is limited.	Unexpected result Higher anxiety testing for multiple conditions May find a mutation in a gene that is not consistent with patient's clinical history	Unexpected result Higher VUS rate Higher anxiety testing for multiple conditions May find a mutation in a gene that is not consistent with patient's clinical history Higher anxiety testing genes without established medical management Even with "positive" result, still need to make medical management recommendations by family history
Benefits	Low VUS rate Results have shortest turn-around-time Clear medical management guidelines	Low VUS rate Cost and time efficient Most have clear medical management guidelines More information for those whose insurance covers genetic testing once in a lifetime May identify contributory mutation in families who have unclear clinical presentations May identify multiple hereditary factors contributing to cancer risk in families, thus enabling risk assessments to be more accurate May identify mutation in clinically actionable gene which will help guide medical management (i.e. identification of additional cancer risks)	Cost and time efficient Provides the most information for those whose insurance covers genetic testing once in a lifetime May identify contributory mutation in families who have unclear clinical presentations May identify multiple hereditary factors contributing to cancer risk in families, thus enabling risk assessments to be more accurate May identify mutation in clinically actionable gene which will help guide medical management (i.e. identification of additional cancer risks)