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Clinician-Reported Impact of Germline Multigene Panel Testing on Cancer Risk Management Recommendations

Carolyn Horton, MS (ID),[1,*] Kirsten Blanco, BS,[1] Min-Tzu Lo, PhD,[1] Virginia Speare, PhD,[1] Holly LaDuca, MS (ID),[1] Jill S. Dolinsky, MS (ID),[1] Allison W. Kurian, MD, MSc (ID)[2]

[1]Ambry Genetics, Aliso Viejo, CA, USA; and [2]Department of Medicine and of Epidemiology and Population Health, Stanford University School of Medicine, Stanford, CA, USA

*Correspondence to: Carolyn Horton, MS, 1 Enterprise, Aliso Viejo, CA 92656, USA (e-mail: chorton@ambrygen.com).

Abstract

Background: With increased adoption of multi-gene panel testing (MGPT) for hereditary cancer, management guidelines now include a wider range of predisposition genes. Yet little is known about whether MGPT results prompt changes to clinicians' risk management recommendations and whether those recommendations adhere to guidelines. **Methods:** We assessed cancer risk management recommendations made by clinicians ordering MGPT for hereditary cancer at a diagnostic laboratory using an internet-based survey. We received paired pre- and posttest responses for 2172 patients (response rate = 14.3%). Unpaired posttest responses were received in 168 additional patients with positive results. All tests were 2-sided. **Results:** Clinicians reported a change in risk management recommendations for 76.6% of patients who tested positive for a pathogenic or likely pathogenic variant, with changes to surveillance being most common (71.1%), followed by surgical (33.6%), chemoprevention (15.1%), and clinical trial (9.4%) recommendations. Clinicians recommended risk-reducing interventions more often for patients with pathogenic variants in high-risk than moderate-risk genes (P < .001), whereas surveillance recommendations were similar for high-risk and moderate-risk genes. Guideline adherence was high for surveillance (86.3%) and surgical (79.6%) recommendations. Changes to risk management recommendations occurred in 8.8% and 7.6% of patients with uncertain and negative results, respectively. **Conclusions:** Clinicians report frequent changes to cancer risk management recommendations based on positive results in both high-risk and moderate-risk genes. Reported introduction of interventions in patients with inconclusive and negative results is rare and adherence to practice guidelines is high in patients with positive results, suggesting a low probability of harm resulting from MGPT.

Germline genetic testing for hereditary cancer predisposition syndromes provides risk stratification and allows clinicians to personalize patients' cancer treatment and risk management. In recent years, there has been a shift towards larger gene panel testing rather than a more targeted, gene-specific approach (1,2). The increased adoption of multi-gene panel testing (MGPT) to identify high-risk patients has led to refined cancer estimates for numerous susceptibility genes (2,3). Genes such as *ATM*, *BRIP1*, *CHEK2*, *MUTYH*, *NBN*, *NF1*, *PALB2*, *RAD51C*, and *RAD51D* have all been shown to confer a greater than twofold risk for breast, ovarian, or colorectal cancer. Consequently, cancer risk estimates have been incorporated by the National Comprehensive Cancer Network (NCCN) into the development of management guidelines for these moderate-risk genes along with high-risk genes such as *APC*, *BRCA1/2*, and Lynch syndrome genes (4,5).

When genes included on MGPT correspond to management guidelines, the increase in diagnostic yield provided by MGPT theoretically increases the clinical utility of testing. However, few empirical data exist on whether NCCN recommendations are being implemented following receipt of results, especially for patients with pathogenic variants in genes other than *BRCA1/2* and Lynch syndrome. Recent studies have indicated that 70%-83% of patients with pathogenic variants (PVs) in moderate-penetrance MGPT genes have had a change in cancer risk management due to their PV result (6-8). Additionally, 79%-82% of interventions that patients reported their physicians recommending were consistent with published guidelines (8). These studies addressed the impact that moderate-penetrance PVs had on physician recommendations, but they did not compare results with the impact of high-penetrance PVs. Therefore, many questions remain about how management changes and

guideline adherence are influenced by gene penetrance and intervention type. To address these questions, we present initial findings of an ongoing study aimed to assess changes in cancer risk management recommendations prompted by MGPT results, using clinician-reported data on an individual patient level.

Methods

Survey and Study Population Description

Clinicians were invited to participate in an institutional review board-exempt (Western Institutional Review Board) study using an online survey to assess cancer risk management recommendations before and after MGPT. Management recommendations pertaining to the following 5 areas were assessed: 1) surveillance, 2) risk-reducing surgery, 3) chemoprevention, 4) clinical trial eligibility, and 5) education and counseling. Pretest survey invitations were emailed to clinicians by the testing laboratory, Ambry Genetics (Aliso Viejo, CA), on submission of each MGPT order. Clinicians who completed the pretest survey were then emailed a posttest survey on results disclosure. Because the majority of changes to management were expected to arise in individuals with PVs, we sought to expand the cohort of individuals who tested positive with PVs. Beginning in February 2020, posttest surveys were sent to any clinician who had received a positive MGPT result in any gene even if no pretest survey was completed, provided the clinician had not opted out of the study. The detailed survey submission workflow is shown in Figure 1. Demographic and clinical information, including age, sex, self-reported race or ethnicity, personal history of cancer, and family history of cancer, was curated from the test requestion form and supporting clinical documents (ie, clinic notes, pathology reports, pedigrees) submitted by the ordering provider at the time of test order. Racial or ethnic groups were categorized as African American or Black, Ashkenazi Jewish, Asian, Hispanic, non-Hispanic White, Other (Brazilian, Middle Eastern, Native American, Portuguese, Sephardic Jewish, and multiple races or ethnicities), and unknown or not provided.

MGPT Result Classification

Interpretation of sequence variations was performed according to the American College of Medical Genetics and Genomics guidelines (9). Variants identified by MGPT were classified as pathogenic, likely pathogenic, Variant of Unknown Significance (VUS), likely benign, or benign according to the Ambry 5-tier variant classification protocol (10). Pathogenic and likely pathogenic variants were defined as positive results. Case s with VUS in the absence of a pathogenic or likely pathogenic variant were defined as inconclusive. Cases with likely benign or benign findings in the absence of a pathogenic, likely pathogenic, and VUS finding were defined as negative. For the purposes of this study, *MUTYH* monoallelic carriers were included in the positive results group due to the existence of NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines), whereas *NTHL1* and *CFTR* monoallelic carriers were excluded from analysis.

New Management Changes

Reported changes in cancer risk management recommendations were compared across overall test result status (positive, inconclusive, negative) and personal history of cancer.

Increases in or introduction of interventions and decreases in or discontinuation of interventions were both assessed. Adjustment in the age of onset, frequency, or type of intervention (ie, analog or digital mammogram vs tomosynthesis or 3D mammogram) was also scored as a change. A copy of the pre- and posttest survey is provided in the Supplementary Methods (available online). Differences between recommendations for patients with positive results in high-risk vs moderate-risk genes were tested in the same way. High- and moderate-risk designations were made based on NCCN Guidelines in place during the study period such that genes specifically designated as high risk by NCCN and/or those with surgical recommendations were categorized as high risk, and the remaining genes were categorized as moderate risk (Table 1) (1,2). Table 1 was adapted with permission from the NCCN Guidelines for Breast/Ovarian Genetic/Familial High-Risk Assessment V3.2019 and Colorectal Genetic/Familial High-Risk Assessment V1.2019. The NCCN Guidelines and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new data becomes available.

Guideline Adherence

For patients with positive results, recommended interventions (mammogram, breast magnetic resonance imaging [MRI], colonoscopy, risk-reducing mastectomy [RRM], and risk-reducing salpingo-oophorectomy [RRSO]) that were included in pre- or posttest responses were compared with the NCCN Guidelines to determine adherence. Guideline adherence was defined as the proportion of patients eligible for a recommended intervention who 1) were already undergoing the intervention based on the pretest response, or 2) had it newly recommended based on posttest response. Therefore, males were excluded from calculations about breast and ovarian cancer, and patients who had already undergone surgical intervention (RRM, RRSO, colectomy) were excluded from surveillance calculations for that cancer site.

Statistical Analysis

The P values of all comparisons were derived from χ^2 test or Fisher's exact test if any observed cell count was less than 10. The odds ratios (ORs) and 95% confidence intervals (CIs) of recommendations between high-risk and moderate-risk genes were calculated based on unconditional maximum likelihood estimation and normal approximation (Wald) confidence interval, respectively. A 2-sided t test was used to compare mean ages between individuals with *CHEK2* PVs and *AMT* PVs. P values less than .05 were considered statistically significant.

Results

Survey Responses and Test Results

Pretest surveys were sent to clinicians based on 14 987 test orders and responses were received for 3233 of these orders (response rate = 21.6%). Corresponding posttest surveys were sent for 3155 orders, and responses were received for 2172 (response rate = 68.9%). An additional 168 posttest-only surveys (without matched pretest surveys) were received for patients with

A

Pre-test invite
sent
N = 14 987

Link active for 14 days

Link active for 14 days

Link active for 14 days

No new test
invites sent

Active opt out
N = 365

Auto opt out
>5 pre-test invites
sent without response
N = 11 389

Pre-test response
received
N = 3233

No new invites sent,
but link remains
active for 14 days

No pre-test
response received,
all survey links
expire

Response received
before 5th invitation
expires; removed
from auto opt out

Test results
reported?
N = 3233

Yes

No

Post-test
invite sent
N = 3155

Link active for
60 days

No post-test
invite sent (i.e.
test cancelled)
n = 78

Post-test
response
received
N = 2144

No response,
link expires

Provider can continue responding
to pre-test invites
or opt out via email link
or stop responding to pre-test
invites to be auto opted out

B

No invitation sent
N = 365

If active opt out

Positive test
results reported
N = 3158

If pre-test response received

Paired pre- and
post-test
workflow
continues
N = 436

Link active for
60 days

All other positive restults

Post-test response
received
N = 168

Link active for
60 days

Post-test response
received
n = 168

Survey invites
declined via active
opt out

No response,
link expires

Provider can continue
responding to positive
only post-test invites or
opt out via email link

Figure 1. Survey submission and response workflow: **A)** Paired pre- and posttest surveys are administered to providers as depicted here. Pretest surveys include an opt-out link (Active Opt Out). Providers who complete a pretest survey are sent a posttest survey once results are returned. Providers who do not complete 5 consecutive surveys will be opted out (Auto Opt Out). **B)** Posttest surveys are also sent to all providers with a positive multigene panel test (MGPT) result regardless of if a pretest survey was received, unless the provider has actively opted out.

Table 1. Gene groupings[a]

Gene list	Any cancer — High risk	Any cancer — Moderate risk	Any cancer — Limited evidence	Breast — High-risk (mammo/MRI 20–25 y age to initiate varies by gene), RRM	Breast — Moderate-risk mammo/MRI 30–40 y (age to initiate varies by gene), no RRM	Breast — Limited evidence no breast guidelines	Colon — High-risk colonoscopy 10–25 y (age to initiate varies by gene)	Colon — Moderate-risk colonoscopy 30–40 y (age to initiate varies by gene)	Ovarian — Increased risk (RRSO/BSO)
APC truncating (n = 6)	Yes	—	—	—	—	—	Yes	—	—
APC p. I1307K[b] (n = 17)	—	Yes	—	—	—	—	—	Yes	—
ATM (n = 34)	—	Yes	—	—	Yes	—	—	—	—
BARD1 (n = 3)	—	—	Yes	—	—	Yes	—	—	—
BLM (n = 3)	—	—	Yes	—	—	Yes	—	—	—
BMPR1A (n = 1)	Yes	—	—	—	—	—	Yes	—	—
BRCA1 (n = 45)	Yes	—	—	Yes	—	—	—	—	Yes
BRCA2 (n = 72)	Yes	—	—	Yes	—	—	—	—	Yes
BRIP1 (n = 12)	—	Yes	—	—	—	Yes	—	—	Yes
CDH1[c] (n = 2)	—	Yes	—	—	Yes	—	—	—	—
CHEK2[b,d] (n = 87)	—	Yes	—	—	Yes	—	—	Yes	—
FANCC (n = 3)	—	—	Yes	—	—	Yes	—	—	—
GREM1 (n = 1)	Yes	—	no	—	—	—	Yes	—	—
MLH1 (n = 8)	Yes	—	—	—	—	—	Yes	—	Yes
MSH2 (n = 9)	Yes	—	—	—	—	—	Yes	—	Yes
MSH6 (n = 16)	Yes	—	—	—	—	—	Yes	—	—
MRE11A (n = 3)	—	—	Yes	—	—	Yes	—	—	—
MUTYH biallelic (n = 5)	Yes	—	—	—	—	—	Yes	—	—
MUTYH monoallelic[b] (n = 36)	—	Yes	—	—	—	—	—	Yes	—
NBN[e] (n = 10)	—	Yes	—	—	Yes	—	—	—	—
NF1[f] (n = 3)	—	Yes	—	—	Yes	—	—	—	—
PALB2 (n = 18)	—	Yes	—	—	Yes	—	—	—	-
PMS2 (n = 16)	Yes	—	—	—	—	—	Yes	—	—
PTEN (n = 4)	Yes	—	—	Yes	—	-	—	Yes	—
RAD50 (n = 5)	—	—	—	—	—	—	—	—	—
RAD51C (n = 7)	—	Yes	Yes	—	—	Yes	—	—	Yes
RAD51D (n = 3)	—	Yes	—	—	—	Yes	—	—	Yes
TP53 (n = 4)	Yes	—	—	Yes	—	—	—	—	—
XRCC2 (n = 1)	—	—	Yes	—	—	Yes	—	—	—
Others (n = 48)	—	—	—	—	—	—	—	—	—

a Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast/Ovarian Genetic/Familial High-Risk Assessment V3.2019 and Colorectal Genetic/Familial High-Risk Assessment V1.2019. BSO = bilateral salpingo-oophorectomy; mammo = mammogram; MRI = magnetic resonance imaging; RRM = risk-reducing mastectomy; RRSO = risk-reducing salpingo-oophorectomy.

b The strength of evidence supporting this categorization is not well-established.

c CDH1: Strong evidence supporting increased risk of lobular breast cancer.

d CHEK2: With predisposition for estrogen receptor+ disease. Risk data are based only on frameshift pathogenic or likely pathogenic variants. The risks for most missense variants are unclear, but for some pathogenic or likely pathogenic variants, such as Ile157Thr, the risk for breast cancer appears to be lower. Management should be based on best estimates of cancer risk for the specific pathogenic or likely pathogenic variant.

e NBN: Management recommendations are based on data derived from the 657del5 Slavic truncating pathogenic or likely pathogenic variant. Although risks for other pathogenic or likely pathogenic variants have not been established, it is prudent to manage patients with other truncating pathogenic or likely pathogenic variants similarly to those with 657del5.

f At this time, there are no data to suggest an increased breast cancer risk after age 50 years. Screening recommendations only apply to individuals with a clinical diagnosis of neurofibromatosis.

Table 2. Population description[a]

| Characteristic	Study population	Overall lab cohort
Sex, No. (%)		
Male	379 (16.2)	12 658 (13.4)
Female	1961 (83.8)	81 396 (86.5)
Age at testing, y		
Mean (SD)	53.0 (14.5)	53.2 (14.1)
Race and ethnicity, No. (%)		
African American/Black	187 (8.0)	7281 (7.7)
Ashkenazi Jewish	127 (5.4)	4066 (4.3)
Asian	108 (4.6)	4787 (5.1)
Hispanic	154 (6.6)	6794 (7.2)
Non-Hispanic White	1561 (66.7)	57 641 (61.3)
Other or unknown	93 (4.0)	13 249 (14.1)
Personal history of cancer, No. (%)		
Yes	1449 (61.9)	63 911 (66.6)
No	877 (37.5)	31 948 (33.3)
Not provided	14 (0.6)	95 (0.1)
Provider type, No. (%)		
Genetic counselor	236 (71.7)	NA
Nurse practitioner/physician assistant	40 (12.1)	NA
Registered nurse	19 (5.8)	NA
Physician	26 (7.9)	NA
Test result, No. (%)		
Positive	470 (20.1)	11 618 (12.4)
Positive (paired pre- and posttest responses only)	302 (13.9)	11 618 (12.4)
Inconclusive	562 (24.0)	25 612 (27.2)
Negative	1298 (55.5)	55 958 (59.5)

[a]NA = not applicable.

positive results. These 2340 surveys were completed by 329 unique clinicians. Most respondents were genetic counselors (71.7%), and the median number of completed surveys per clinician was 2 (range = 1-145). Most patients were female (83.8%; 16.2% male), non-Hispanic White (66.7%; 8.0% African American or Black, 5.4% Ashkenazi Jewish, 4.6% Asian, 6.6% Hispanic, 4.0% Other, unknown, or not provided), and had a personal history of cancer (61.9%), consistent with frequencies reported in other hereditary cancer MGPT cohorts (3,11). Among patients about whom surveys were returned, 470 had positive results (20.1%), 562 had inconclusive results (VUS; 24.0%), 1298 had negative results (55.5%), and 10 were carriers (CFTR, NTHL1) (Table 2).

New Management Changes

Clinicians reported making at least 1 results-related change to cancer risk management based on test results for 76.6% of patients with positive results, 8.8% with inconclusive results, and 7.6% with negative results (Figure 1). Thus, recommended changes were statistically significantly more likely to be reported in patients with positive results compared with inconclusive and negative results (OR = 37.99, 95% CI = 28.93 to 49.85, $P < .001$). There was no statistically significant difference in the frequency of reported changes in patients with inconclusive compared with negative results (OR = 1.20, 95% CI = 0.84 to 1.71, $P = .32$). There was a decrease in or discontinuation of interventions in 0.8%, 2.9%, and 1.6% of patients with positive, negative, and inconclusive results, respectively. Based on these low numbers, a more detailed assessment of decrease in interventions was not performed.

Among patients with positive results, recommendations about surveillance were the most frequently reported change (71.1%), followed by recommendations about surgery (33.6%), chemoprevention (15.1%), and clinical trials (9.4%) (Figure 2). There were no statistically significant differences in recommendations for surveillance ($P = .75$), surgery (0.71), chemoprevention ($P = .45$), or clinical trials ($P = .61$) between responses from genetic counselors and other provider types. Individuals without a personal history of cancer were slightly more likely to have any change to recommendations reported (OR = 1.6, 95% CI = 1.03 to 2.53, $P = .04$); however, there were no statistically significant differences in these groups when comparing specific intervention types. Clinicians reported changes in surveillance recommendations at similar rates for patients with pathogenic variants in high-risk compared with moderate-risk genes (OR = 1.22, 95% CI = 0.77 to 1.93, $P = .39$). More specifically, there was no difference in the proportion of individuals with increases or additions to mammogram or breast MRI recommendations between high- and moderate-risk breast cancer genes or increases or additions to colonoscopy recommendations between high- and moderate-risk colon cancer genes (Table 3). In contrast, clinicians reported higher rates of changes in recommendations for surgery (OR = 6.18, 95% CI = 3.97 to 9.60, $P < .001$), chemoprevention (OR = 4.12, 95% CI = 2.33 to 7.27, $P < .001$), and clinical trials (OR = 5.42, 95% CI = 2.43 to 12.08, $P < .001$) for patients with pathogenic variants in high-risk compared with moderate-risk genes.

Changes to cancer management recommendations prompted by positive test results were not always uniform among genes with similar guidelines (Tables 4-6). For example, clinicians reported discussing RRSO more frequently for
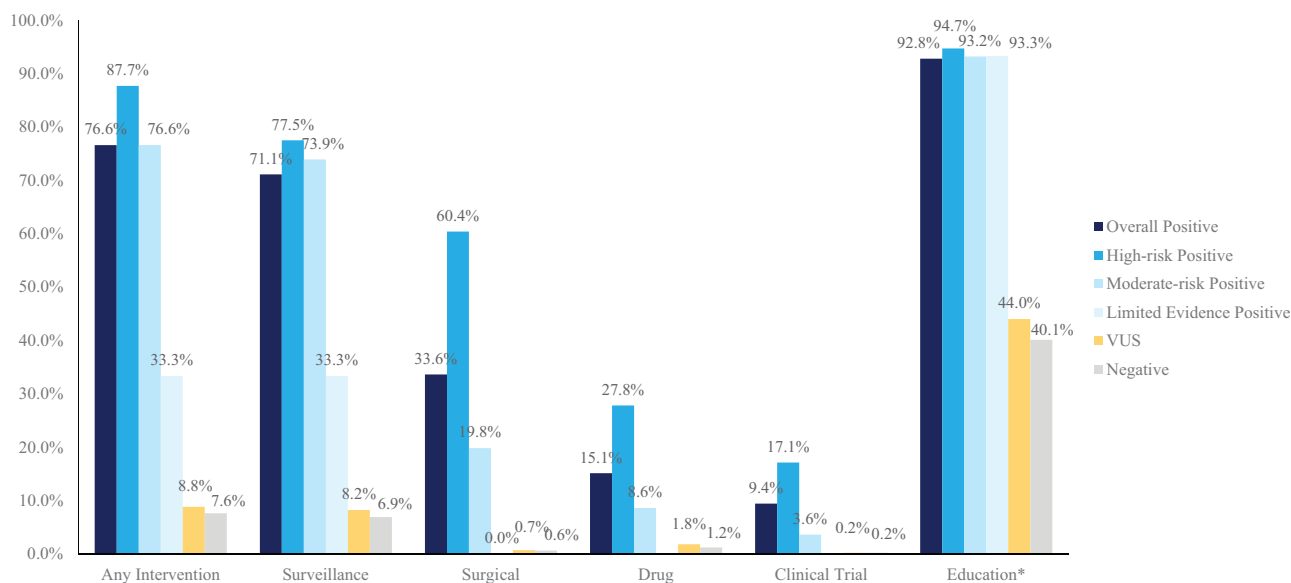
Figure 2. Reported management change by type. *Education includes referral to a specialist, risk counseling, family member identification, and symptom awareness. VUS = variant of unknown significance.

Table 3. Differences in recommendation introduction between cancer risk groups

Intervention	High-risk cancer genes, %	Moderate-risk cancer genes, %	Difference in recommendation discussion?	P[a]
Breast cancer				
Mammogram	56.0	46.4	No	.11
Breast MRI	67.2	68.2	No	.86
RRM	61.6	20.5	Yes	<.001
Colon cancer				
Colonoscopy	79.0	71.1	No	.24

[a]P values derived from χ^2 test or Fisher's exact test if any observed cell count was less than 10. No adjustments were made for multiple comparisons. All tests were 2-sided. MRI = magnetic resonance imaging; RRM = risk-reducing mastectomy.

patients with pathogenic variants in *BRCA1/2* than other genes with RRSO recommendations (*BRIP1, MLH1, MSH2, RAD51C,* and *RAD51D*) (OR = 2.66, 95% CI = 1.27 to 5.58, P = .01). We also observed that *CHEK2* pathogenic variants were less likely to prompt a change in mammogram recommendations compared with other moderate-risk breast cancer genes (P = .01), even when excluding the moderately penetrant p. I157T variant. However, based on pretest survey responses, patients with *CHEK2* PVs were more likely to have a mammogram already included in their reported recommendations before receiving their positive result than patients with PVs in other moderate-risk breast genes (54.0% vs 33.8%; P = .01), so receipt of *CHEK2* PV results did not require a change to mammography recommendations. Individuals with *CHEK2* PVs were not statistically significantly older (P = .64) or more likely to be affected with breast cancer (P = .67) than individuals with PVs in other moderate-risk breast genes, so the reason for higher rates of pretest mammogram in this group may be due to personal or family medical history that was not assessed in this study. In addition, patients with monoallelic *MUTYH* PVs were less likely to have a change in colonoscopy recommendations compared with other moderate-risk colon cancer genes (P < .001). This observation is likely due to guidelines requiring that a patient have a first-degree relative with colon cancer to recommend increased surveillance, given that 86.4% of those *MUTYH* carriers without reported colonoscopy recommendations did not have a family history of colon cancer.

Clinicians reported discussing RRM with 20.5% of patients with PVs in moderate-risk breast cancer genes that lacked a guideline recommendation for RRM. A statistically significantly higher proportion of these patients had a personal history of breast cancer compared with those without RRM discussion (OR = 2.92, 95% CI = 1.23 to 76.97, P = .01); thus, treatment of an active cancer diagnosis may have influenced surgical decision making, and this was not a prophylactic surgery only. Furthermore, RRM discussion was introduced to a majority of patients with *CDH1* or *PALB2* PVs (12 of 20, 60.0%) but rarely in patients with other moderate-risk breast cancer genes (19 of 132, 14.4%). In fact, clinicians' rates of discussing RRM for patients with PVs in *PALB2* (a moderate-risk gene) were more similar to their rates of discussing RRM with high-risk genes (OR = 0.78, 95% CI = 0.28 to 2.31, P = .62) rather than other moderate-risk genes (OR = 6.86, 95% CI = 2.30 to 20.44, P < .001). *CDH1* recommendations were not evaluated independently due to small numbers (n = 2).

Guideline Adherence

Guideline adherence calculations were performed in 302 patients with PVs for whom paired pre- and posttest survey responses were returned. The overall adherence rate to guidelines based on survey responses was 86.31% (95% CI = 83.24% to 89.93%) for surveillance recommendations and 79.64% (95%

Table 4. Gene-specific differences in breast cancer risk management changes[a]

Gene	Mammogram					Breast MRI					RRM				
	Individuals with PV	Compared with high-risk breast genes		Compared with moderate-risk breast genes		Individuals with PV	Compared with high-risk breast genes		Compared with moderate-risk breast genes		Individuals with PV	Compared with high-risk breast genes		Compared with moderate-risk breast genes	
	No. intervention recommended/No. with PV per gene (%)	No. intervention recommended/No. with high-risk PV (%)	p[b]	No. intervention recommended/No. with moderate risk PV (%)	p[b]	No. intervention recommended/No. with high-risk PV (%)	No. intervention recommended/No. with moderate-risk PV (%)	p[b]	No. intervention recommended/No. with high-risk PV (%)	p[b]	No. intervention recommended/No. with moderate-risk PV (%)	No. intervention recommended/No. with moderate-risk PV (%)	p[b]	No. intervention recommended/No. with moderate-risk PV (%)	p[b]
BRCA1/BRCA2	67/117 (57.3)	NA		70/151 (46.4)	.08	78/117 (66.7)	NA		103/151 (68.2)	.79	73/117 (62.4)	NA		31/151 (20.5)	<.001
ATM	17/32 (53.1)	70/125 (56.0)	.77	51/117[c] (43.6)	.34	22/32 (68.8)	84/125 (67.2)	.87	79/117[c] (67.5)	.90	7/32 (21.9)	77/125 (61.6)	<.001	24/117[c] (20.5)	.87
CHEK2 (including p. I157T)	26/79 (32.9)	70/125 (56.0)	.001	39/65[c] (60.0)	.01	50/79 (63.3)	84/125 (67.2)	.57	49/65[c] (75.4)	.12	9/79 (11.4)	77/125 (61.6)	<.001	20/65[c] (30.8)	.006
CHEK2 (excluding p. I157T)	17/56 (30.4)	70/125 (56.0)	.001	39/65[c] (60.0)	.001	35/56 (62.5)	84/125 (67.2)	.54	49/65[c] (75.4)	.13	7/56 (12.5)	77/125 (61.6)	<.001	20/65[c] (30.8)	.02
NBN	6/9 (66.7)	70/125 (56.0)	.73	63/141[c] (44.7)	.30	7/9 (77.8)	84/125 (67.2)	.72	95/141[c] (67.4)	.72	1/9 (11.1)	77/125 (61.6)	.004	29/141[c] (20.6)	.69
PALB2	10/16 (62.5)	70/125 (56.0)	.79	60/133[c] (45.1)	.29	12/16 (75.0)	84/125 (67.2)	.78	90/133[c] (67.7)	.78	9/16 (56.3)	77/125 (61.6)	.79	21/133[c] (15.8)	<.001

[a]Patients with more than 1 co-occurring pathogenic variant are removed from gene-specific totals. NA represent calculations limited to genes with n greater than 5. MRI = magnetic resonance imaging; PV = pathogenic variant; RRM = risk-reducing mastectomy.

[b]P values derived from χ^2 test or Fisher's exact test if any observed cell count was less than 10. No adjustments were made for multiple comparisons. All tests were 2-sided.

[c]Specified gene removed from analysis.

CI = 77.36% to 89.64%) for surgical recommendations. Adherence to mammography guidelines was observed for 89.06% (95% CI = 81.42% to 96.71%) of patients with high-risk pathogenic variants and 90.24% (95% CI = 83.82% to 96.67%) of patients with moderate-risk pathogenic variants, and adherence to breast MRI guidelines was observed with 85.94% (95% CI = 77.42% to 94.45%) of high-risk pathogenic variants and 80.49% (95% CI = 71.91% to 89.07%) of moderate-risk pathogenic variants. Responses were adherent to guidelines for discussion of RRM and RRSO in 79.69% (95% CI = 69.83% to 89.54%) and 8% (95% CI = 73.20% to 90.43%) of eligible pathogenic variants carriers. Colonoscopy was included in recommendations for 96.43% (95% CI = 89.55% to 100.00%) of patients with positive results in high-risk colorectal genes and for 77.57% (95% CI = 69.67% to 85.47%) of patients with positive results in moderate-risk colorectal genes. No differences in adherence rates for mammogram (P = 1.0), breast MRI (P = .57), RRM (0.32), RRSO (P = .22), or colonoscopy (P = .31) were observed between responses from genetic counselors compared with other provider types.

Discussion

This study provides insight into how clinicians are using genetic testing to inform management of inherited cancer risks. In this survey-based study of clinicians ordering MGPT, positive genetic test results frequently prompted changes to cancer risk management recommendations. This was observed for both high- and moderate-risk genes that predispose to a variety of cancer types. Notably, clinicians reported that pathogenic variants in moderate penetrance genes ATM, CHEK2, NBN, NF1, and PALB2 prompted a change in their recommendations as often as did pathogenic variants in BRCA1/2. Appropriately, changes to surgical or chemoprevention recommendations were reported more frequently in patients with pathogenic variants in high- vs moderate-risk genes, and introduction of recommendations not specified in published guidelines were rare.

A slightly lower guideline adherence rate was observed for surgical compared with surveillance recommendations; however, our study did not capture clinical factors such as advanced disease and contraindications to invasive risk-reducing procedures. Despite this, changes in recommendations were largely adherent to published guidelines for both high- and moderate-risk genes. These findings suggest that clinicians are accurately interpreting MGPT results, referring to existing guidelines, and making appropriate recommendations accordingly.

Some results may signal the level of confidence that clinicians have in published guidelines or the strength of evidence supporting cancer risk estimates for a given gene. For example, clinicians were twice as likely to recommend RRSO in patients with PVs in BRCA1/2 vs PVs in BRIP1, MLH1, MSH2, RAD51C, or RAD51D. This could be due to several contributing factors, such as a less comprehensive understanding of ovarian cancer association with non-BRCA1/2 genes and/or ambiguity in guideline language ("recommend" vs "consider" RRSO). Other factors such as personal cancer history, family cancer history, and existing interventions before genetic testing likely influence clinicians' recommendations, as demonstrated by more RRM discussions in patients with breast cancer and fewer colonoscopy recommendations in MUTYH carriers without family history of colon cancer, and fewer changes to mammogram recommendations in patients with CHEK2 PVs. Clinicians recommended RRM for more than one-half of patients with PALB2 PVs and all patients

Table 5. Gene-specific differences in colorectal cancer risk management changes[a]

	Individuals with PV	Colonoscopy			
		Compared with high-risk colorectal genes		Compared with moderate-risk colorectal genes	
Gene	No. intervention recommended/ No. with PV per gene (%)	No. intervention recommended/ No. with high-risk PV (%)	P[b]	No. intervention recommended/No. with moderate-risk PV (%)	P[b]
APC truncating	3/5 (60.0)	45/56[c] (80.4)	.29	101/142 (71.1)	.63
MLH1/MSH2	13/16 (81.3)	35/45[c] (77.8)	1.0	101/142 (71.1)	.56
MSH6	11/15 (73.3)	37/46[c] (80.4)	.72	101/142 (71.1)	1.0
PMS2	12/14 (85.7)	35/46[c] (76.1)	.71	101/142 (71.1)	.35
APC p. I1307K	13/16 (81.3)	49/62 (79.0)	1.0	87/125[c] (69.6)	.40
CHEK2 (incuding p. I157T)	65/79 (82.3)	49/62 (79.0)	.63	31/57[c] (54.4)	<.001
CHEK2 (excluding p. I157T)	46/56 (82.1)	49/62 (79.0)	.67	31/57[c] (54.4)	.002
MUTYH monoallelic	13/34 (38.3)	49/62 (79.0)	<.001	86/104[c] (82.7)	<.001

[a]Patients with more than 1 co-occurring pathogenic variant were removed from gene-specific totals. Calculations limited to genes with n greater than 5; PV = pathogenic variant.
[b]P values derived from χ^2 test or Fisher's exact test if any observed cell count was less than 10. No adjustments were made for multiple comparisons. All tests were 2-sided.
[c]Specified gene removed from analysis.

Table 6. Gene-specific differences in ovarian cancer risk management changes[a]

	Individuals with PV	RRSO	
		Compared with other increased risk ovarian genes	
Gene	No. intervention recommended/No. with PV per gene (%)	No. intervention recommended/No. with PV (%)	P[b]
BRCA1/BRCA2	78/117 (66.7)	17/39[c] (43.6)	.01
BRIP1	5/11 (45.5)	89/144[c] (61.8)	.34
MLH1/MSH2	6/16 (37.5)	89/139[c] (64.0)	.06
RAD51C/D	5/10 (50.0)	90/146[c] (61.6)	.51

[a]Patients with more than 1 co-occurring pathogenic variant were removed from gene-specific totals. Calculations limited to genes with n greater than 5. PV = pathogenic variant; RRSO = risk-reducing saplingo-oophorectomy.
[b]P values derived from χ^2 test or Fisher's exact test if any observed cell count was less than 10. No adjustments were made for multiple comparisons. All tests were 2-sided.
[c]Specified gene removed from analysis.

with *CDH1* PVs despite the fact that guidelines cite insufficient evidence to recommend surgery for both of these genes. This may indicate that clinicians augment their interpretation of guidelines with other data sources, because studies have indicated that *PALB2* PVs and *CDH1* PVs have breast cancer penetrance similar to *BRCA2* PVs (12,13) and that detection of lobular breast cancer, which is associated with *CDH1* PVs, is challenging with standard imaging techniques such as mammogram (14). Such gene-specific results can identify areas of need for continued evidence accumulation, guideline development, and clinician education.

One potential risk associated with genetic testing is the misinterpretation of VUS results as PVs, which could lead to unwarranted interventions. Previous studies reported frequent use of risk-reducing surgery among patients with VUS results (15). Here, we found that clinicians responded similarly to negative and inconclusive results; reports of inconclusive results prompting surgical or medical intervention were rare. This may be due in part to the high proportion of genetic counselors among survey participants and suggests a benefit from expert oversight of genetic testing and results interpretation.

Our study has limitations. The low response rate and high proportion of genetic counselors among survey respondents limits the generalizability of these findings to the oncology community as a whole. Many patients undergo genetic testing for cancer risk without encountering a genetic counselor, and thus aspects of the current results may not fully translate to less specialized care settings (16). However, we observed that management changes and guideline adherence were similar between genetic counselors and other provider types. Another limitation is self-selection by clinicians who opted into the study (especially given a relatively low response rate), because they may differ in practice patterns from those who did not. However, the patients represented in this survey dataset are representative of the laboratory's broader population of MGPT recipients with respect to demographics and results distribution (Table 2). Further, potential biases were reduced by controlling for unique respondents, provider type, and patient demographics in multivariable modeling.

These results have implications for clinical practice and health policy. In general, they offer assurance that ordering clinicians report appropriate and guideline-adherent recommendations, which supports the clinical utility and low probability of harm associated with MGPT. However, clinicians' reported management changes represent a short-term measure in the continuum of care and longer follow-up of health

outcomes for patients with hereditary cancer predisposition syndromes is critical. As information on the clinical validity (3,17) and cost-effectiveness (18) of MGPT emerges, so must data on the actionability of such testing. Results of this study can contribute to these efforts and expedite the development of evidence-based management guidelines.

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Data Availability

The data that support the findings of this study are available on request from the corresponding author, CH, with reasonable privacy restrictions.

References

1. Kurian AW, Ward KC, Howlader N, et al. Genetic testing and results in a population-based cohort of breast cancer patients and ovarian cancer patients. *J Clin Oncol*. 2019;37(15):1305–1315.
2. LaDuca H, Polley EC, Yussuf A, et al. A clinical guide to hereditary cancer panel testing: evaluation of gene-specific cancer associations and sensitivity of genetic testing criteria in a cohort of 165,000 high-risk patients. *Genet Med*. 2020;22(2):407–415.
3. Rosenthal ET, Bernhisel R, Brown K, Kidd J, Manley S. Clinical testing with a panel of 25 genes associated with increased cancer risk results in a significant increase in clinically significant findings across a broad range of cancer histories. *Cancer Genet*. 2017;218-219:58–68.
4. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast/Ovarian Genetic/Familial High-Risk Assessment V3.2019. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed June 28, 2019. www.NCCN.org.
5. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colorectal Genetic/Familial High-Risk Assessment V1.2019. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed July 9, 2019. www.NCCN.org.
6. Bunnell AE, Garby CA, Pearson EJ, Walker SA, Panos LE, Blum JL. The clinical utility of next generation sequencing results in a community-based hereditary cancer risk program. *J Genet Couns*. 2017;26(1):105–112.
7. Eliade M, Skrzypski J, Baurand A, et al. The transfer of multigene panel testing for hereditary breast and ovarian cancer to healthcare: what are the implications for the management of patients and families? *Oncotarget*. 2017;8(2):1957–1971.
8. Hall ET, Divya P, Caswell-Jin J, et al. Pathogenic variants in less familiar cancer susceptibility genes: what happens after genetic testing? *J Clin Oncol Precis Oncol*. 2018;2(2):1–10.
9. Richards S, Aziz N, Bale S, et al.; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405–424. doi:10.1038/gim.2015.30.
10. Pesaran T, Karam R, Huether R, et al. Beyond DNA: an integrated and functional approach for classifying germline variants in breast cancer genes. *Int J Breast Cancer*. 2016;2016:2469523. doi: 10.1155/2016/2469523.
11. Neben CL, Zimmer AD, Stedden W, et al. Multi-gene panel testing of 23,179 individuals for hereditary cancer risk identifies pathogenic variant carriers missed by current genetic testing guidelines. *J Mol Diagn*. 2019;21(4):646–657.
12. Roberts ME, Ranola JMO, Marshall ML, et al. Comparison of CDH1 penetrance estimates in clinically ascertained families vs families ascertained for multiple gastric cancers. *JAMA Oncol*. 2019;5(9):1325–1331. doi: 10.1001/jamaoncol.2019.1208.
13. Yang X, Leslie G, Doroszuk A, et al. Cancer risks associated with germline PALB2 pathogenic variants: an international study of 524 Families. *J Clin Oncol*. 2020;38(7):674–685. doi:10.1200/J Clin Oncol.19.0190
14. Wilson N, Ironside A, Diana A, Oikonomidou O. Lobular breast cancer: a review. *Front Oncol*. 2021;10:591399.
15. Kurian AW, Li Y, Hamilton AS, et al. Gaps in incorporating germline genetic testing into treatment decision-making for early-stage breast cancer. *J Clin Oncol*. 2017;35(20):2232–2239.
16. Katz SJ, Ward KC, Hamilton AS, et al. Gaps in receipt of clinically-indicated genetic counseling after diagnosis of breast cancer. *J Clin Oncol*. 2018;36(12):1218–1224.
17. Lee K, Seifert BA, Shimelis H, et al. Clinical validity assessment of genes frequently tested on hereditary breast and ovarian cancer susceptibility sequencing panels. *Genet Med*. 2019;21(7):1497–1506.
18. Sun L, Brentnall A, Patel S, et al. A cost-effectiveness analysis of multigene testing for all patients with breast cancer. *JAMA Oncol*. 2019;5(12):1718–1730.