Clinical Utility of Hereditary Cancer Panel Testing: Impact of PALB2, ATM, CHEK2, NBN, BRIP1, RAD51C, and RAD51D Results on Patient Management and Adherence to Provider Recommendations

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BACKGROUND: Although management guidelines exist for several genes associated with a 2-fold to 5-fold increase in the relative risk for certain cancers, the value of testing for them remains controversial. METHODS: De-identified personal and family history data for 654 individuals with pathogenic variants (PVs) in PALB2, ATM, CHEK2, NBN, BRIP1, RAD51C, and/or RAD51D were analyzed for pretest and post-test candidacy for guideline-recommended management of cancer risk. These individuals were invited to complete a survey about provider recommendations and their adherence. RESULTS: Twenty-four percent of CHEK2, ATM, PALB2, or NBN PV carriers were appropriate for consideration of annual breast magnetic resonance imaging screening before genetic testing, with the remaining 76% appropriate only after testing. No BRIP1, RAD51C, or RAD51D PV carriers were appropriate for consideration of risk-reducing salpingo-oophorectomy before genetic testing; 100% were appropriate only after testing. Seventeen percent of CHEK2 PV carriers were appropriate for earlier and more frequent colonoscopy before genetic testing, with the remaining 83% appropriate only after testing. Provider recommendations for annual breast magnetic resonance imaging, consideration of risk-reducing salpingo-oophorectomy, and earlier and more frequent colonoscopy were reported by 42%, 26%, and 66% of breast, ovarian, and colorectal cancer risk PV carriers, respectively, before genetic testing, versus 82%, 79%, and 81%, respectively, after testing. Nearly all respondents had planned or undertaken provider-recommended management. CONCLUSIONS: Testing for PALB2, ATM, CHEK2, NBN, BRIP1, RAD51C, and RAD51D changed management for those carrying PVs. Provider recommendations were aligned with guidelines, and patients adhered to recommendations, both of which are critical for reducing both long-term cancer morbidity and mortality. Cancer 2020;126:549-558. © 2019 Myriad Genetics, Inc. Cancer published by Wiley Periodicals, Inc. on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

KEYWORDS: breast cancer, cancer risk, colorectal cancer, hereditary cancer, ovarian cancer.

INTRODUCTION
Pathogenic variants (PVs) in several cancer predisposition genes are known to confer various levels of risk. The most well known are BRCA1 and BRCA2, but several others are clinically important in assessing patients’ cancer risk. PVs in PALB2, ATM, CHEK2, NBN, BRIP1, RAD51C, and RAD51D are associated with a 2-fold to 5-fold increase in relative risk for certain cancers.1-5 However, because of cancer syndrome heterogeneity, it is often difficult for providers to determine which cancer predisposition genes to test in a patient whose family or personal history is suggestive of a hereditary cancer syndrome. Multigene panels have become clinically available and commonly ordered because they address syndrome overlap and more effectively identify individuals with PVs than testing for PVs using a single-syndrome approach.4-7

The growth in evidence characterizing cancer risk for individuals with PVs in PALB2, ATM, CHEK2, NBN, BRIP1, RAD51C, and RAD51D has led to the publication of clinical guidelines for managing such patients. National Comprehensive Cancer Network (NCCN) guidelines recommend consideration of annual breast magnetic resonance imaging (MRI) and mammography for individuals with PALB2, ATM, CHEK2, and/or NBN PVs1; consideration of risk-reducing salpingo-oophorectomy (RRSO) for individuals with BRIP1, RAD51C, and/or RAD51D PVs1; and earlier and more frequent colonoscopy for individuals with CHEK2 PVs.2

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Clinical actionability of multigene panel testing for genes other than *BRCA1* and *BRCA2* has been the focus of several recent studies. One found that the use of a multigene panel to identify individuals with PVs yielded information that would change management recommendations in approximately one-half of the individuals tested. In addition, at least 1 relative would be appropriate for genetic testing in more than one-half of the families of individuals with PVs. In another study, testing for breast cancer risk genes other than *BRCA1* and *BRCA2* increased clinically actionable findings by 66%, and three-quarters of these findings were in women who would not have been otherwise eligible for more aggressive screening. Despite the promising findings of these studies, the use of multigene panels in clinical practice continues to be questioned. Although the increased cancer risk associated with PVs in *PALB2, ATM, CHEK2, NBN, BRIP1, RAD51C, and RAD51D* has been demonstrated, these genes have not been studied as extensively as *BRCA1* and *BRCA2*. Also, compared with testing for *BRCA1* and *BRCA2*, testing for these genes has occurred on a smaller scale and in less diverse populations. Traditional clinical utility endpoints, such as improved long-term survival and reduced mortality, take decades to measure, so the relatively recent release of management recommendations for PV-positive individuals has led to interim measures of actionability, such as the potential for the test result to change medical management. These data gaps are likely part of the reason why guidelines recommend “consideration” of management changes in PV carriers versus the more direct recommendation language for management change in those carrying PVs in *BRCA1* and *BRCA2*.

In the current study, we sought to add to the growing body of evidence that testing for *PALB2, ATM, CHEK2, NBN, BRIP1, RAD51C, and RAD51D* changes clinical management beyond that based on a patient’s personal and family history alone. Furthermore, we assessed whether health care providers recommended management according to guidelines and the extent to which patients adhered to such recommendations, because such assessments are important for understanding the real-world effectiveness of guidelines intended to improve cancer morbidity and mortality.

**MATERIALS AND METHODS**

*Institutional Review Board Approval*

This study was reviewed and designated as exempt by Western Institutional Review Board.

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**Study and Control Cohorts**

To establish a study cohort, the Myriad Women’s Health (formerly Counsyl Inc) internal database was queried for patients who: 1) underwent testing with a 29-gene hereditary cancer panel (Reliant; Counsyl Inc) between March 2016 and March 2018; 2) were age ≥18 years; 3) had a germline pathogenic or likely pathogenic variant identified (referred to throughout as PV) in *PALB2, ATM, CHEK2, NBN, BRIP1, RAD51C*, and/or *RAD51D*; and 4) had not opted out of being involved in research (Fig. 1). A control cohort was generated using the same criteria, except that it included those who did not have a pathogenic or likely pathogenic variant identified in any gene ordered by the provider (Fig. 1). The study and control cohorts were further validated by ensuring that individuals’ email addresses were included in their patient record, did not contain formatting errors, did not match that of a provider, or were not associated with multiple requisitions. After all validation, 654 individuals constituted the study cohort, and >10,000 individuals constituted the control cohort (Fig. 1). At this stage, the study and control cohorts were de-identified by assigning each individual a numerical code in place of identifying information. In addition, email addresses were decoupled from the test result and from other identifying information for use in the survey described below, resulting in a list of email addresses for PV-positive and PV-negative individuals (but not including the genotype or demographic information of each individual).

**Determination of Pretest and Post-Test Enhanced Management for Individuals With PVs**

Pretest and post-test management analysis (Fig. 1, blue box) was performed using the recommendations detailed in Supporting Table 1. Briefly, pretest management was determined by retrospectively applying management recommendations based on the personal and family cancer histories that were in place at the time of data analysis to the 654 individuals with PVs. Post-test management was determined by retrospectively applying NCCN management recommendations based on hereditary cancer panel test results that were in place at the time of data analysis to the 654 individuals with PVs.

**Survey Development and Execution**

Survey questions are included in Supporting Figure 1. Questions were programmed into commercial software (Logician; Decision Analyst Inc) to optimize survey administration and response collection. Questions were pretested with 7 individuals meeting the survey or control cohort eligibility requirements to determine understandability, optimal wording, and completion of questions as intended.
The survey was fielded by Decision Analyst, Inc between July 27, 2018 and August 13, 2018. The 654 individuals in the study cohort were invited by email to participate in an online survey (Fig. 1, yellow boxes). After invitations were sent, 32 emails were undeliverable, effectively reducing the survey study cohort to 622 individuals. One thousand individuals from the 10,000 individuals control cohort were randomly selected and invited to participate in 2 waves of 500; access to the survey was disabled after completion by 150 respondents (a sample size that approximately matched the study cohort) (Fig. 1, yellow boxes). Study cohort participants were eligible to receive or donate a $50 incentive upon completion of the survey. Control cohort participants were eligible to receive or donate a $25 incentive.

**Data Analysis**

Survey data management and tabulation were accomplished using UNCLE (The Uncle Group, Inc), and analyses were performed using SPSS software (IBM Corporation). For pretest and post-test management and survey results, descriptive statistics were used to describe differences. Statistical significance between proportions was determined using chi-square analysis; a result was considered significant for $P < .05$.

**RESULTS**

**Study Participants**

Six hundred fifty-four individuals with a PV in *PALB2*, *ATM*, *CHEK2*, *NBN*, *BRIP1*, *RAD51C*, and/or *RAD51D* were identified as eligible to participate in the study (Table 1). The average age of individuals with PVs was 49 years; 95% (n = 620) were women, 92% (n = 599) had a family history of any cancer, and 39% (n = 256) had a personal history of any cancer (Table 1).

Of the 622 individuals with PVs who were reached with a survey invitation, 161 completed it, resulting in a response rate of 26%. One hundred forty-nine individuals without PVs completed the survey. With the exception of genetic test results, most demographic and clinical characteristics were not significantly different between the PV-positive and PV-negative survey respondent groups; the PV-positive respondent group included significantly fewer individuals with a family history of ovarian, fallopian, or peritoneal cancers than the PV-negative respondent group (Table 1).

**Changes in Management Directed by Genetic Test Results**

Among 560 individuals with PVs in *CHEK2*, *ATM*, *PALB2*, or *NBN*, 386 were eligible for consideration of
### TABLE 1. Participant Characteristics

| Characteristic                         | Database Cohort   | Survey Respondents | PV-Negative |
|----------------------------------------|-------------------|--------------------|-------------|
| **No. (%)**                            |                   |                    |             |
| **Total no.**                          | 654               | 161                | 149         |
| **Age: Average [range], y**            | 49 [18-88]        | 48 [18-76]         | 48 [21-79]  |
| **Sex**                                |                   |                    |             |
| Women                                  | 620 (95)          | 157 (98)           | 144 (97)    |
| Men                                    | 34 (5.0)          | 4 (2.0)            | 5 (3.0)     |
| **Ethnicitya**                         |                   |                    |             |
| Other/mixed Caucasian                  | 227 (35)          | 59 (37)            | 25 (17)     |
| Northern European                      | 169 (26)          | 64 (40)            | 61 (41)     |
| Ashkenazi Jewish                       | 33 (5.0)          | 9 (5.6)            | 15 (10)     |
| African or African American            | 28 (4.3)          | 3 (1.9)            | 8 (5.4)     |
| Hispanic                               | 23 (3.5)          | 7 (4.3)            | 13 (8.7)    |
| Southern European                      | 19 (2.9)          | 11 (6.8)           | 13 (8.7)    |
| East Asian                             | 6 (0.9)           | 1 (0.6)            | 3 (2.0)     |
| Middle Eastern                         | 5 (0.8)           | 1 (0.6)            | 2 (1.3)     |
| French Canadian or Cajun               | 4 (0.6)           | 2 (1.2)            | 4 (2.7)     |
| South Asian                            | 4 (0.6)           | 2 (1.2)            | 2 (1.3)     |
| Native American                        | 3 (0.5)           | 6 (3.7)            | 7 (4.7)     |
| Southeast Asian                        | 2 (0.3)           | 2 (1.2)            | 3 (2.0)     |
| Other/unknown/prefer not to say        | 131 (20)          | 27 (17)            | 28 (19)     |
| **Family history of any cancera**      | 599 (92)          | 153 (95)           | 135 (91)    |
| Breast                                 | 474 (79)          | 128 (84)           | 110 (81)    |
| Colorectal                             | 143 (24)          | 35 (23)            | 32 (24)     |
| Ovarian, fallopian, peritoneal          | 132 (22)          | 29 (19)            | 46 (34)     |
| Other                                  | 367 (81)          | 108 (71)           | 81 (50)     |
| **Personal history of any cancera**    | 256 (39)          | 58 (36)            | 54 (36)     |
| Breast                                 | 171 (67)          | 45 (78)            | 34 (63)     |
| Colorectal                             | 5 (2.0)           | 0 (0.0)            | 2 (3.7)     |
| Ovarian, fallopian, peritoneal          | 22 (8.6)          | 6 (10)             | 4 (7.4)     |
| Other                                  | 93 (36)           | 18 (31)            | 15 (28)     |
| **Individuals with PVs**               | 654 (100)         | 161 (100)          | NA          |
| CHEK2                                  | 303 (46)          | 75 (47)            |             |
| ATM                                    | 133 (20)          | 32 (20)            |             |
| PALB2                                  | 95 (15)           | 28 (17)            |             |
| BRIP1                                  | 54 (8.3)          | 12 (7.5)           |             |
| RAD51C                                 | 25 (3.8)          | 6 (3.7)            |             |
| NBN                                    | 18 (2.8)          | 1 (0.6)            |             |
| RAD51D                                 | 14 (2.1)          | 3 (1.9)            |             |
| >1 Gene                                 | 11 (1.7)c         | 4 (2.5)            |             |
| **Geographic region of residence**     |                   |                    |             |
| Northeast                              | 20 (12)           | 14 (9.0)           |             |
| Midwest                                | 30 (19)           | 25 (17)            |             |
| South                                  | 76 (47)           | 69 (46)            |             |
| West                                   | 35 (22)           | 40 (27)            |             |
| Outside the United States              | 0 (0.0)           | 1 (1.0)            |             |
| **Annual household income**            |                   |                    |             |
| <30,000                                | 5 (3.0)           | 15 (10)            |             |
| $30,000-$49,000                        | 15 (9.0)          | 24 (16)            |             |
| $50,000-$99,000                        | 46 (29)           | 35 (23)            |             |
| >$100,000                              | 57 (35)           | 50 (34)            |             |
| Prefer not to say                      | 36 (24)           | 25 (17)            |             |
| **Highest education attained**         |                   |                    |             |
| Less than bachelor's degree            | 51 (32)           | 48 (32)            |             |
| Bachelor's degree                      | 60 (37)           | 56 (38)            |             |
| Advanced degree                        | 48 (30)           | 41 (28)            |             |
| Prefer not to say                      | 2 (1.0)           | 4 (3.0)            |             |

Abbreviations: NA, not applicable; PV, pathogenic variant.

aTotals equal >100% because more than 1 ethnicity and/or more than 1 cancer could be indicated on the test requisition or the survey.

bProportions were significantly lower than in the PV-negative group ($P < .05$).

cCombinations with >1 gene were: ATM + CHEK2, $n = 3$; ATM + BRIP1, $n = 3$; ATM + RAD51C, $n = 1$; ATM + NBN, $n = 1$; CHEK2 + PALB2, $n = 1$; CHEK2 + BRIP1, $n = 1$; and CHEK2 + RAD51C, $n = 1$.

dThese demographic factors either were not included on the test requisition form or were blinded to investigators. All percentages ≥10% were rounded to the nearest whole number.
annual breast MRI, with eligibility defined as being a women aged <75 years and having no personal history of breast cancer (Table 2).1-3,18,21 By using the Claus model to estimate lifetime risk,18 24% (n = 91) of eligible individuals were appropriate candidates for consideration of annual MRI screening. The remaining 76% (n = 295) were appropriate candidates only after genetic test results were known, representing a significant increase. When analyzed individually, a significant increase in the number of individuals appropriate for consideration of annual MRI screening was seen for those with PVs in CHEK2, ATM, and PALB2 (Table 2).

Among 100 individuals with PVs in BRIPI, RAD51C, or RAD51D, 86 were eligible for consideration of RRSO, with eligibility defined as being a woman and having no personal history of ovarian cancer (including fallopian tube and peritoneal cancers); those with a personal history of ovarian cancer were assumed to have already undergone bilateral oophorectomy as part of cancer treatment (Table 2).21 No consensus management recommendations exist for individuals at average risk or increased risk for ovarian cancer based on family history; therefore, no individuals were deemed appropriate candidates for consideration of RRSO based on family history. One hundred percent (n = 86) of individuals were appropriate candidates for consideration of RRSO only after receiving genetic test results, representing a significant increase. This significant increase was seen for each gene and for cases in which individuals carried more than 1 PV (Table 2).

Among 309 individuals with PVs in CHEK2, 301 were eligible for colonoscopy every 5 years starting at age ≤40 years, depending on family history, with eligibility defined as being aged <75 years (Table 2). On the basis of family or personal history, 17% (n = 50) of eligible individuals would be appropriate candidates for more frequent colonoscopy starting at age ≤40 years, whereas the remaining 83% (n = 251) were appropriate candidates only after receiving genetic test results (Table 2).2 This represents a significant increase in the number of individuals considered appropriate candidates for earlier and more frequent colonoscopy. This significant increase was also seen among individuals who carried a PV in CHEK2 and another gene (Table 2).

**Patient-Reported Provider Management Recommendations and Patient Adherence**

One hundred thirteen individuals with PVs in PALB2, ATM, CHEK2, and/or NBN responded to the survey and were appropriate candidates for consideration of annual breast MRI screening. Individuals who were not women or who had undergone a previous bilateral mastectomy were not considered in this cohort because annual breast MRI screening is not recommended in such cases.22 Before knowing genetic test results, 42% (n = 47) of respondents reported that their providers had recommended annual breast MRI starting immediately or sometime in the future (Fig. 2, pretest) versus 82% (n = 93) after receiving genetic test results (Fig. 2, post-test), representing a significant increase. Among 66 individuals who had received positive genetic test results and for whom providers recommended annual breast MRI immediately, 71% (n = 47) reported that they had already undertaken such screening, and another 26% (n = 17) reported that they planned to undergo such screening in the future (Fig. 3).

Nineteen individuals with PVs in BRIPI, RAD51C, and/or RAD51D responded to the survey and were appropriate candidates for consideration of RRSO. Individuals who were not women were not considered in this cohort, nor were individuals who had a personal history of ovarian cancer because it was assumed that such individuals would already have undergone bilateral oophorectomy as part of cancer treatment.21 Before knowing genetic test results, 26% (n = 5) of respondents reported that their providers had recommended RRSO immediately or sometime in the future (Fig. 2, pretest) versus 79% (n = 15) after receiving genetic test results (Fig. 2, post-test), representing a significant increase. Among 9 individuals who had received positive genetic test results and for whom providers recommended RRSO immediately, 89% (n = 8) reported that they had already undergone the surgery, and the other 11% (n = 1) reported that they planned to undergo the surgery in the future (Fig. 3).

Seventy-seven individuals with a PV in CHEK2 responded to the survey and were appropriate candidates for colonoscopy every 5 years starting at age ≤40 years. Before knowing genetic test results, 66% (n = 51) of respondents reported that their providers had recommended colonoscopy every 5 years immediately or sometime in the future (Fig. 2, pretest) versus 81% (n = 62) after receiving genetic test results (Fig. 2, post-test), representing a significant increase. Among 34 individuals who had received positive genetic test results and for whom providers recommended colonoscopy immediately, 76% (n = 26) reported that they had already undergone the procedure, and the other 24% (n = 8) reported that they planned to undergo the procedure in the future (Fig. 3).
**TABLE 2.** Changes in Candidacy for Enhanced Management Based on Genetic Test Results

| Variable | All Genes | CHEK2 | ATM | PALB2 | NBN | BRIP1 | RAD51C | RAD51D | >1 Gene |
|----------|-----------|-------|-----|-------|-----|-------|--------|--------|---------|
| Total no. of individuals | 654 | 303 | 133 | 95 | 18 | 54 | 25 | 15 | 11 |
| Enhanced breast cancer screening: Annual mammogram and consider annual breast MRI starting at age 40 y (age 30 y for PALB2) or earlier based on family history | | | | | | | | | |
| Individuals with PVs in ATM, CHEK2, PALB2, and/or NBN | 560 | 303 | 133 | 95 | 18 | — | — | — | 11 |
| Eligible for consideration of enhanced breast cancer screening: Women aged <75 y with no personal history of breast cancer | 386 | 209 | 88 | 64 | 16 | — | — | — | 10 |
| Appropriate candidates without genetic testing<sup>a</sup> | 91 (24) | 39 (19) | 20 (23) | 22 (34) | 6 (38) | — | — | — | 5 (50) |
| Appropriate candidates only after genetic testing<sup>b</sup> | 295 (76)<sup>c</sup> | 170 (81)<sup>c</sup> | 68 (77)<sup>c</sup> | 42 (66)<sup>c</sup> | 10 (63) | — | — | — | 5 (50) |
| Ovarian cancer prevention: Consider RRSO at age 45-50 y | | | | | | | | | |
| Individuals with PVs in BRIP1, RAD51C, and/or RAD51D | 100 | — | — | — | — | 54 | 25 | 15 | 6 |
| Eligible for consideration of ovarian cancer prevention: Women with no personal history of ovarian cancer<sup>d</sup> | 86 | — | — | — | — | 45 | 22 | 13 | 6 |
| Appropriate candidates without genetic testing<sup>a</sup> | 0 (0) | — | — | — | — | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Appropriate candidates only after genetic testing<sup>b</sup> | 86 (100)<sup>c</sup> | — | — | — | — | 45 (100)<sup>c</sup> | 22 (100)<sup>c</sup> | 13 (100)<sup>c</sup> | 6 (100)<sup>c</sup> |
| Enhanced colorectal cancer screening: Colonoscopy every 5 y starting at age 40 y or earlier based on family history | | | | | | | | | |
| Individuals with PVs in CHEK2 | 309 | 303 | — | — | — | — | — | — | 6 |
| Eligible for consideration of enhanced colorectal screening: Age <75 y | 301 | 296 | — | — | — | — | — | — | 5 |
| Appropriate candidates without genetic testing<sup>e</sup> | 50 (17) | 49 (17) | — | — | — | — | — | — | 1 (20) |
| Appropriate candidates only after genetic testing<sup>f</sup> | 251 (83)<sup>c</sup> | 247 (83)<sup>c</sup> | — | — | — | — | — | — | 4 (80)<sup>c</sup> |

Abbreviations: MRI, magnetic resonance imaging; PV: pathogenic or likely pathogenic variant, RRSO: risk reducing salpingo-oophorectomy.

<sup>a</sup>Values are based on data from the Claus model (lifetime risk of breast cancer >20%; Claus 1994<sup>18</sup>).

<sup>b</sup>Values are based on National Comprehensive Cancer Network (NCCN) criteria (NCCN 2018, 2019<sup>1,2</sup>).

<sup>c</sup>P < .05.

<sup>d</sup>It was assumed that women with a personal history of ovarian cancer had undergone bilateral oophorectomy (NCCN 2018<sup>21</sup>).

<sup>e</sup>Values are based on data from Tung 2016<sup>3</sup>.
We also analyzed reductions in the number of recommendations made for enhanced management in those found not to be PV carriers. One hundred thirty-three individuals found not to have a PV in *PALB2*, *ATM*, *CHEK2*, and/or *NBN* responded to the survey and were appropriate candidates for consideration of annual breast MRI screening. Before receiving genetic test results, 26% (n = 34) of respondents’ providers had recommended annual breast MRI starting immediately or sometime in the future; and, after receiving negative genetic test results, 24% (n = 32) of respondents’ providers made such a recommendation (Fig. 2).
hundred thirty-nine individuals found not to have a PV in BRIP1, RAD51C, and/or RAD51D responded to the survey and were appropriate candidates for consideration of RRSO. Before receiving genetic test results, 15% (n = 21) of respondents’ providers had recommended RRSO immediately or sometime in the future; and, after receiving negative genetic test results, 6% (n = 9) of respondents’ providers made such a recommendation, representing a significant decrease (Fig. 2). One hundred forty-nine individuals found not to have PV in CHEK2 responded to the survey and were appropriate candidates for colonoscopy every 5 years. Before receiving genetic test results, 53% (n = 79) of respondents’ providers had recommended colonoscopy immediately or sometime in the future; and, after receiving negative genetic test results, 35% (n = 52) of respondents’ providers made such a recommendation, representing a significant decrease (Fig. 2).

DISCUSSION
Our results show that testing for several genes that increase cancer risk provided actionable management information beyond that available by risk assessment based on personal and family history alone. In a large cohort of individuals carrying PVs in PALB2, ATM, CHEK2, NBN, BRIP1, RAD51C, and RAD51D, 76% to 100% were identified as appropriate candidates for enhanced screening or risk-reducing surgery as a result of receiving positive genetic test results. Of the 7 genes studied here, significant increases in candidacy for enhanced screening was seen for all but NBN PV carriers. This may be a function of the small sample size of NBN PV carriers in the current study, but it also may be because of the less robust cancer risk data for NBN relative to data for the other genes in the study.

Our change-in-management results build on previous studies that have supported the actionability of testing for PVs in cancer risk genes other than BRCA1 and BRCA2. In a study of patients who met criteria for hereditary breast and ovarian cancer genetic testing, management recommendations were changed for 25% of patients with PVs in PALB2, ATM, CHEK2, NBN, BRIP1, and RAD51C. This proportion is less than that found in our study, but the cohort was small (40 patients), and nearly all (38 of 40) had been or were currently being treated for a personal history of cancer. By contrast, our PV-positive cohort was more than 15 times larger, and <40% had a personal history of cancer. A much larger study assessed 7 genes known to be associated with a >20% lifetime risk for breast cancer and found that, among those with a PV in ATM, CHEK2, or PALB2, only 21%, 23%, or 27%, respectively, would have been appropriate candidates for enhanced management based on the Claus model alone, similar to our findings. This collective evidence suggests that more individuals are appropriate for enhanced management than can be identified by family and personal history alone.

The current study demonstrates that the majority of providers (79%-82%) recommended management aligned with clinical guidelines and that nearly all patients (97%-100%) adhered to their providers’ recommendations. Although we believe this is the first study to assess such factors for PV carriers in these genes, provider recommendations and patient adherence have been assessed for BRCA1 and BRCA2 PV carriers. A 2011 study found that obstetrician/gynecologist providers recommended breast MRI and RRSO aligned with then-current NCCN guidelines in 89% and 76%, respectively, of unaffected BRCA1 PV carriers. Despite the more recent existence of management guidelines for the genes included in this study compared with studies on BRCA1 and BRCA2, our results are similar, suggesting that providers align their management recommendations with guidelines even when they are relatively recent. Our results showing the decrease in provider recommendations for enhanced screening or surgery in patients found not to carry PVs also are important as they suggest fewer unnecessary procedures and further support provider alignment to management guidelines. Although this study focused mainly on the management of those found to carry PVs, further study of management changes in individuals who test negative for PVs is warranted.

With respect to patients who are identified as appropriate candidates for enhanced screening but whose providers did not recommend enhanced screening (Fig. 2), we can speculate about the reason enhanced management was not recommended. First, the wording of the recommendations may suggest that they are merely suggestive rather than directive. For example, the NCCN recommends consideration of annual breast MRI for PALB2, ATM, CHEK2, and NBN PV carriers and consideration of RRSO for BRIP1, RAD51C, and RAD51D PV carriers. The “consider” modifier in these recommendations may lead providers to interpret them as optional. Second, although the NCCN guidelines recommend enhanced management of those found to carry PVs in the genes studied here, the guidelines do not address testing for the genes in the first place, which may undermine the
importance of enhanced management for those found to carry PVs. Third, patient characteristics and preferences may have made them inappropriate candidates for enhanced management, for example, an inability to access medical centers at which surgery or screening takes place, a perception of low cancer risk, or a personal opposition to surgery or enhanced screening altogether.

Few studies have directly assessed whether a provider recommendation of cancer screening or risk-reducing procedures drives patient adherence. In one study, approximately one-half of high-risk patients who were referred for BRCA1 and BRCA2 testing adhered to guidelines for breast self-examination, breast MRI, transvaginal ultrasound, and CA-125 screening, whereas 80% to 90% adhered to guidelines for clinical breast examination, mammogram, breast ultrasound, and pelvic examination. Among patients who did not adhere to guidelines, the most commonly cited reason was that their provider had not recommended the management. These findings underscore the importance of the provider’s recommendation for patient adherence and the potential to improve outcomes when provider recommendations are aligned with guidelines. Although long-term outcome studies are needed to determine the effect of testing for PALB2, ATM, CHEK2, NBN, BRIP1, RAD51C, and RAD51D on cancer morbidity and mortality, our study suggests that NCCN-recommended management for carriers of PVs in these genes is correctly recommended by providers and adhered to by patients.

Our study has limitations that should be noted. First, we retrospectively applied family and personal cancer history information noted on the test requisition to determine appropriate management before genetic testing. We have assumed that family and personal cancer history information is accurate because it was indicated by the patient’s provider, but we cannot guarantee its veracity in every case because it was not confirmed by medical records. Second, the test requisition provided enough information to apply the Claus model for breast cancer risk. It is possible that additional risk factors, such as those assessed by the Tyrer-Cuzick model (eg, age of menarche, age at first live birth), may have increased the number appropriate for enhanced management before genetic testing. However, the Claus model is well validated for assessing primary breast cancer risk, and it is completely reliant on family history to determine risk, which is the main factor relied upon by guidelines to identify appropriate candidates for annual MRI screening. Third, the survey portion of this study relied on patients to recall their providers’ management recommendations and their own adherence. Patient memory can sometimes be inaccurate and, although we pretested the questions, patients may interpret them in different ways. Fourth, the demographics of our study cohort skewed toward nonminority individuals who were well educated and had moderate to high incomes; these factors may have favorably affected access to testing and management. Related to this limitation, we could not collect demographic information on survey nonresponders and cannot determine whether responders were representative of the cohort invited to participate in the survey. And fifth, we cannot rule out response bias; those who chose to respond to the survey invitation may have represented individuals more likely to follow their providers’ recommendations.

The data here show that testing for PALB2, ATM, CHEK2, NBN, BRIP1, RAD51C, and RAD51D changes patient management strategies for those carrying PVs and better informs provider recommendations compared with risk assessment based on personal and family cancer history alone. Furthermore, provider recommendations were aligned with guidelines, and patients adhered to such recommendations, both of which are critical in reducing cancer morbidity and mortality over the long term.

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AUTHOR CONTRIBUTIONS
Valentina Vysotskaia: Conceptualization, formal analysis, investigation, methodology, visualization, writing—original draft, and writing—review and editing. K. Eerik Kaseniit: Conceptualization, data curation, formal analysis, investigation, methodology, validation, visualization, and writing—review and editing. Leslie Bucheit: Formal analysis, methodology, visualization, and writing—review and editing. Kaylene Ready: Conceptualization, data curation, formal analysis, investigation, methodology, supervision, visualization, and writing—review and editing. Kristin Price: Conceptualization, formal analysis, investigation, methodology, visualization, and writing—review and editing. Katherine Johansen Taber: Conceptualization, formal analysis, investigation, methodology, supervision, visualization, writing—original draft, and writing—review and editing.

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