Association of Polygenic-Based Breast Cancer Risk Prediction With Patient Management

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ABSTRACT

PURPOSE Breast cancer (BC) risk prediction is more accurate when clinical and polygenic factors are combined (combined risk score [CRS]), but little is known about how CRS results affect real-world patient management.

METHODS Deidentified medical and pharmacy claims data were linked with Tyrer-Cuzick (TC) and CRS results and evaluated for BC risk management. Patients were divided into subcohorts on the basis of lifetime risk predicted by CRS and by TC ("+": ≥20% risk, "−": <20%): CRS+ TC+, CRS+ TC−, CRS− TC+, and CRS− TC−. Claims data related to screening mammography (SM) in patients younger than 40 years, breast magnetic resonance imaging (MRI), and genetic counseling (GC) were compared 360 days before and after CRS testing. Differences in pre- and post-CRS management were evaluated using McNemar tests, and post-CRS management of subcohorts was compared using multivariable logistic regression.

RESULTS After CRS testing, the CRS+ TC+, CRS+ TC−, and CRS− TC+ subcohorts had 1.6-2.2-fold increases in SM in patients younger than 40 years (all $P < .02$) and 4.7-5.6-fold increases in breast MRI (all $P < .001$). The CRS+ TC+ and CRS+ TC− subcohorts had 1.9-2.3-fold increases in GC (both $P < .001$). SM in those younger than 40 years, breast MRI, and GC did not increase in the CRS− TC− subcohort. After CRS testing, compared with the CRS− TC− subcohort, the CRS+ TC+, CRS+ TC−, and CRS− TC+ subcohorts had significantly higher odds of receiving SM before age 40 years (odds ratio [OR], 3.80-5.19), breast MRI (OR, 11.55-23.09), and GC (OR, 2.03-2.91; all $P < .001$).

CONCLUSION Patients with ≥20% lifetime risk predicted by either CRS or TC were more likely to receive enhanced management compared with those who had <20% lifetime risk, suggesting that clinicians considered the CRS in BC risk management.

ACCOMPANYING CONTENT

Data Supplement

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INTRODUCTION

Pathogenic variants in high- and moderate-penetrance breast cancer (BC)–associated genes can increase lifetime BC risk to as high as 87%.[1-6] However, only approximately 5%-10% of BC cases are attributable to such single-gene variants.[7] Many cases are likely influenced by the aggregate effect of single-nucleotide polymorphisms (SNPs), of which hundreds related to BC risk have been identified.[8,9] Individually, these SNPs are associated with modest levels of risk, but together, are associated with risks comparable with single-gene high- and moderate-penetrance pathogenic variants.[10-13]

In current clinical practice, BC screening and preventive measures are guided by risk calculators such as the Tyrer-Cuzick (TC) model, which has been clinically validated for individualized risk assessment on the basis of age, family history, height, weight, breast density, history of hormone use, and other factors.[12] However, the prediction of individual BC risk has evolved as the genetic contributions to risk have been identified. Polygenic risk scores (PRSs) aggregate the effects of SNPs to assess an individual's predisposition to developing a disease.[13,14] Studies have demonstrated that PRSs can predict an individual's risk of developing BC, particularly when combined with clinical factors, including age, family history, and personal cancer history, used in traditional risk calculation models.[10,11,15-19] For example, a validation study of a 149-SNP PRS combined with the TC risk calculator (combined risk score [CRS]) in a cohort of nearly 90,000 females demonstrated that it was well calibrated, accurate, and significantly enhanced BC risk prediction

CONTEXT

Key Objective
To assess how breast cancer (BC) risk management changes after patients undergo risk assessment on the basis of a polygenic risk score combined with clinical factors (combined risk score [CRS]).

Knowledge Generated
Patients with a ≥20% lifetime risk of BC predicted by a CRS were significantly more likely to have enhanced screening (mammography before age 40 years and breast magnetic resonance imaging) and genetic counseling than those with <20% lifetime risk. Patient management appeared to align with that recommended by guidelines when increased risk was predicted by a CRS.

Relevance
Use of a CRS to determine BC risk may lead to screening appropriate for individual risk level.

accuracy compared with the TC risk model alone.[15] A follow-up longitudinal study of the CRS in more than 130,000 females who were unaffected with BC at the time of testing showed that the CRS was a better predictor of incident BC than the TC model alone.[20] Incorporating BC PRSs into risk assessment may offer a more precise estimation of risk and, therefore, more tailored approaches to screening and management.

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines) emphasize the importance of stratifying patients by risk level to optimize screening intervals and modalities.[21] The guidelines recommend that females with a lifetime risk of BC ≥20% undergo annual screening mammography (SM) beginning as early as age 30 years and annual breast magnetic resonance imaging (MRI) screening beginning as early as age 25 years, along with consideration of genetic counseling (GC) to guide risk assessment and management decisions.[21] Additionally, both the NCCN and US Preventive Services Task Force recommend that patients at high risk be offered risk-reducing medication (chemoprevention), such as tamoxifen, raloxifene, and aromatase inhibitors.[22,23] Guidelines do not recommend consideration of prophylactic mastectomy unless patients have risk in the range of that conferred by pathogenic variants in high-penetrance genes, such as *BRCA1* and *BRCA2*.[22]

NCCN recommends that BC risk be estimated using models that are largely dependent on family history, such as BRCAPRO, TC, and BOADICEA/CanRisk.[22,24-26] Although recent versions of TC and BOADICEA incorporate PRS-based risk estimates, NCCN discourages the routine use of PRSs in risk assessment and suggests that they need additional validation research.[22] However, the demonstrated predictive ability of CRSs has led to their clinical availability.[15,20] Little is known about how clinicians use CRS results in real-world practice. In this retrospective analysis of insurance claims data, we studied the real-world uptake of several BC risk surveillance and management measures in the 360 days after clinician and patient receipt of a validated BC CRS.[15,20]

METHODS

Data Set Generation

A data set was generated by linking patient data from Myriad Genetics, Inc, including RiskScore results and patient clinical data collected on the test request form, to an administrative claims data set from the Optum Labs Data Warehouse (OLDW), which includes longitudinal health information on commercially insured and Medicare Advantage enrollees across the United States. RiskScore is a CRS that combines BC risk SNPs with clinical factors in TC,[15] and is offered to females who are eligible for testing with the MyRisk hereditary cancer panel. RiskScore results are calculated for those who do not carry pathogenic variants in BC risk–associated genes on MyRisk (other than *CHEK2*) and do not have a personal history of BC, lobular carcinoma in situ, hyperplasia, atypical hyperplasia, or an unknown breast biopsy result. The version of RiskScore used during the majority of the study period combined 86 BC risk SNPs with TC v7.0.2.[24,27] During the last approximately 6 months of the study period, RiskScore expanded to include 149 BC risk and genetic-ancestry SNPs combined with clinical risk factors in TC v7.0.2.[15,24] To conduct the linkage, the Myriad and OLDW data sets were deidentified according to the Health Insurance Portability and Accountability Act standards and tokenized using Datavant.[28] Expert determination was used to minimize the risk that the linked data could result in patient reidentification. Because all data used for the study were deidentified in a compliant manner, this study did not meet the US Department of Health and Human Services definition of research on human subjects (HHS 46.102) and did not require institutional review board approval.

Study Cohort

The final study cohort was created by applying the following criteria to the linked data set (Fig 1 and the Data Supplement, Fig S1): patients received RiskScore results between August 1, 2017, and November 30, 2021 (the identification period); had continuous medical and pharmacy benefits for ≥360 days before and ≥360 days after the index date (the date the CRS result was reported to the ordering clinician); were age 18 years and older at the index date; did not have information on the test request form or medical claims indicating a history of breast malignancy, BC, or any metastatic cancer

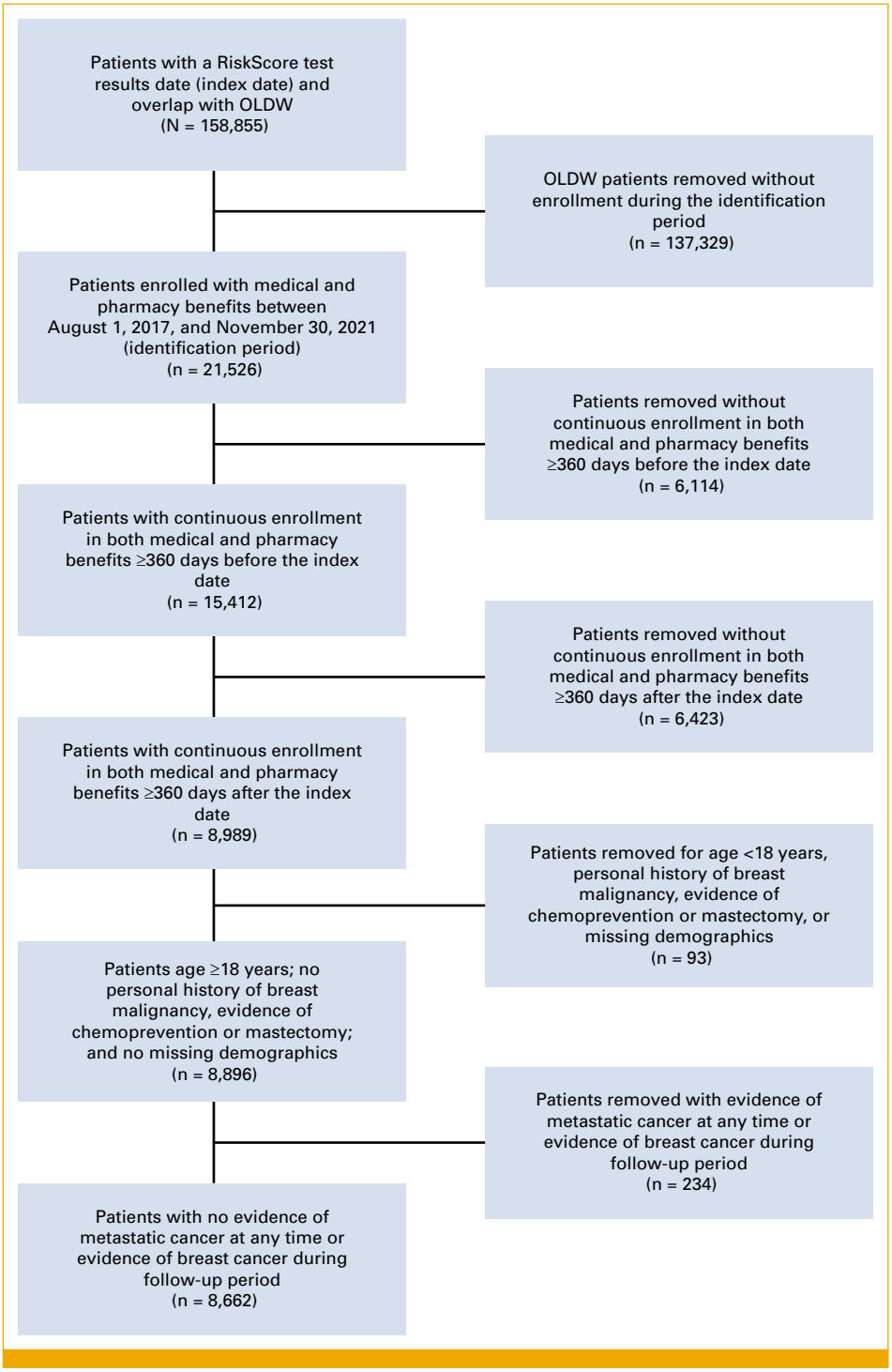

FIG 1. Study sample attrition. Out of 158,855 patients with a CRS result and present in the OLDW data set, 8,662 met the study inclusion and exclusion criteria. CRS, combined risk score; OLDW, Optum Labs Data Warehouse.

before the index date; did not have medical claims or medication prescription fills indicating BC prevention measures (tamoxifen, raloxifene, aromatase inhibitors, premenopausal ovarian function suppression, or mastectomy) before the index date; did not have medical claims of BC diagnosis after the index date; and did not have missing demographic information. Codes associated with inclusion/exclusion criteria are listed in the Data Supplement (Tables S1 and S2). Patients located in Alaska, Colorado, Florida, New Hampshire, New York, Oklahoma, Oregon, South Dakota, Minnesota, Michigan, or Nebraska were excluded because of state-based restrictions on genetic data use.

Patients were grouped into four subcohorts on the basis of their lifetime risk of BC predicted by the CRS and TC: CRS ≥20% and TC ≥20% (referred to in this study as CRS+ TC+), CRS ≥20% and TC <20% (CRS+ TC−), CRS <20% and TC ≥20% (CRS− TC+), and CRS <20% and TC <20% (CRS− TC−).

Assessment of Patient Management

Patient management measures assessed during a 360-day baseline period (the period before the index date) and a 360-day follow-up period (the period after the index date) were SM, breast MRI, and GC; chemoprevention and mastectomy were assessed only in the follow-up period as patients with these measures in the baseline period were excluded. Because SM is recommended by some guidelines for all females beginning at age 40 years,[21] assessment of SM in this study was restricted to those younger than 40 years. Codes and medications used to indicate management are listed in the Data Supplement (Tables S1 and S2).

Statistical Analysis

McNemar tests were conducted to compare management in the baseline and follow-up periods within each subcohort. Management outcomes during the follow-up period were also compared across subcohorts (CRS+ TC+, CRS+ TC−, CRS− TC+, and CRS− TC−) using multivariable logistic regression models. Separate models were developed to analyze SM in patients younger than 40 years, breast MRI, and GC. All models were adjusted for the year of CRS test (coded as a categorical variable), ancestry (White *v* non-White), menopausal stage (premenopausal, perimenopausal, postmenopausal, or missing), and test type (MyRisk full panel or BC risk-focused subpanel *v* a colorectal cancer risk-focused subpanel). Models predicting breast MRI and GC included additional categorical variables for age (<40, 40-60, >60), and Quan-Charlson comorbidity index (0-2 *v* >2). For models predicting SM in patients younger than 40 years, the Quan-Charlson comorbidity index was categorized as 0 versus 1+. In a post hoc analysis, pairwise differences between all possible pairs of subcohort odds ratios were tested using a Tukey correction to control for Type I errors.

RESULTS

Of 158,855 patients in the linked data set, 8,662 met inclusion criteria (Fig 1). Average patient age was 46 years (standard deviation [SD], 12), with nearly 95% (8,216) younger than 65 years (Table 1). For the first 4 years of the identification period, the CRS was validated only for females of European descent; accordingly, >94% (8,186) of the cohort self-reported their ethnicity as White. Slightly more than half of the patients (3,702) with known menopausal status were premenopausal, nearly 15% (1,295) had a personal history of cancer other than breast, and nearly one third (2,857) had a first-degree relative with BC (Table 1).

Among the 8,662-patient cohort, 2,423 (28.0%) had a lifetime BC risk of ≥20% predicted by both the CRS and TC (CRS+ TC+), 696 (8.0%) ≥20% by the CRS and <20% by TC (CRS+ TC−), 856 (9.9%) <20% by the CRS and ≥20% by TC (CRS− TC+), and 4,687 (54.1%) <20% by both the CRS and TC (CRS− TC−; Table 1). Mean CRS-predicted lifetime risk of BC in each group was 29.9% (SD, 7.9%), 24.5% (SD, 4.3%), 16.4% (SD, 2.6%), and 11.2% (SD, 4.4%), respectively (Table 1). The CRS reclassified risk for 1,552 (17.9%) patients; it predicted lifetime risk <20% in 856 (26.1%) of the 3,279 patients in whom TC predicted ≥20%, and it predicted lifetime risk ≥20% in 696 (12.9%) of the 5,383 patients in whom TC predicted <20%.

Management of Patients After CRS Results

SM (<40 years)

In patients younger than 40 years (n = 2,799), during the baseline period, 11.89%, 7.69%, 8.84%, and 4.99% of those in the CRS+ TC+, CRS+ TC−, CRS− TC+, and CRS− TC− subcohorts had a SM, respectively. In the follow-up period, those percentages significantly increased to 18.54% (P < .001), 16.60% (P = .003), and 14.36% (P = .017) in the CRS+ TC+, CRS+ TC−, and CRS− TC+ subcohorts, respectively (Table 2 and Fig 2). By contrast, the percentage of those in the CRS− TC− subcohort receiving SM in the follow-up period did not significantly change compared with baseline (4.37%, P = .46).

In the follow-up period, the three subcohorts having ≥20% lifetime risk predicted by the CRS and/or TC were 3.8-5.2 times more likely to receive SM (<40 years) compared with the CRS− TC− subcohort (Data Supplement, Table S3). Pairwise comparisons of the three subcohorts with high risk predicted by CRS and/or TC did not identify any significant differences between these groups (Table 3).

Breast MRI

During the baseline period, 3.43%, 2.59%, 2.34%, and 0.94% of those in the CRS+ TC+, CRS+ TC−, CRS− TC+, and CRS−

TABLE 1. Baseline Demographics of Study Cohort

Baseline Characteristic	Total (N = 8,662; 100%)	CRS+ TC+ (n = 2,423; 28.0%)	CRS+ TC− (n = 696; 8.0%)	CRS− TC+ (n = 856: 9.9%)	CRS− TC− (n = 4,687; 54.1%)
Age, years, mean (SD)	45.74 (12.07)	41.22 (10.48)	44.58 (10.88)	41.96 (10.43)	48.94 (12.30)
18-44, No. (%)	4,075 (47.04)	1,491 (61.54)	345 (49.57)	507 (59.23)	1,732 (36.95)
<40, No. (%)	2,799 (32.30)	1,068 (44.08)	247 (35.49)	362 (42.29)	1,122 (23.94)
45-64, No. (%)	4,141 (47.81)	921 (38.01)	337 (48.42)	>338 (>39.49)	<2,545 (<52.30)
65+, No. (%)	446 (5.15)	11 (0.45)	14 (2.01)	<11 (<1.29)	>410 (>8.75)
Geography, No. (%)					
Northeast	660 (7.62)	163 (6.73)	64 (9.20)	62 (7.24)	371 (7.92)
Midwest	2,090 (24.13)	586 (24.18)	152 (21.84)	195 (22.78)	1,157 (24.69)
West	1,131 (13.06)	324 (13.37)	88 (12.64)	124 (14.49)	595 (12.69)
South	4,781 (55.20)	1,350 (55.72)	392 (56.32)	475 (55.49)	2,564 (54.70)
Type of insurance coverage, No. (%)					
Commercial	8,249 (95.23)	2,408 (99.38)	683 (98.13)	>845 (>98.71)	<4,313 (<92.02)
Medicare advantage	413 (4.77)	15 (0.62)	13 (1.87)	<11 (<1.29)	>374 (>7.98)
Quan-Charlson comorbidity index,[a] mean (SD)	0.37 (0.96)	0.20 (0.58)	0.35 (0.83)	0.25 (0.70)	0.49 (1.14)
0, No. (%)	6,950 (80.24)	>2,084 (>86.01)	>540 (>77.59)	>711 (>83.06)	<3,615 (<77.13)
1-2, No. (%)	1,395 (16.10)	307 (12.67)	126 (18.10)	120 (14.02)	842 (17.96)
3-4, No. (%)	222 (2.56)	21 (0.87)	19 (2.73)	14 (1.64)	168 (3.58)
5+, No. (%)	95 (1.10)	<11 (<0.45)	<11 (<1.58)	<11 (<1.29)	>62 (>1.32)
Race, No. (%)					
Asian	17 (0.20)	<17 (<0.70)	0 (0.00)	<17 (<1.99)	<17 (<0.37)
Black	74 (0.85)	>19 (>0.78)	<11 (<1.58)	<11 (<1.29)	>33 (>0.70)
Hispanic	56 (0.65)	<11 (<0.45)	<11 (<1.58)	<11 (<1.29)	>23 (>0.49)
White	8,186 (94.50)	2,296 (94.76)	651 (93.53)	811 (94.74)	4,428 (94.47)
Other	329 (3.80)	91 (3.76)	37 (5.32)	34 (3.97)	167 (3.56)
Menopause stage,[b] No. (%)					
Pre	3,702 (54.12)	1,417 (72.41)	297 (56.46)	456 (68.37)	1,532 (41.52)
Post	2,372 (34.68)	334 (17.07)	166 (31.56)	130 (19.49)	1,742 (47.21)
Peri	766 (11.20)	206 (10.53)	63 (11.98)	81 (12.14)	416 (11.27)
Personal cancer history, No. (%)	1,295 (14.95)	181 (7.47)	88 (12.64)	65 (7.59)	961 (20.50)
Limited family structure,[c] No. (%)	218 (7.90)	55 (6.89)	16 (7.17)	26 (8.70)	121 (8.40)
First-degree relative breast cancer, No. (%)	2,857 (32.98)	1,649 (68.06)	177 (25.43)	421 (49.18)	610 (13.01)
First-degree relative ovarian cancer, No. (%)	847 (9.78)	99 (4.09)	75 (10.78)	51 (5.96)	622 (13.27)
CRS lifetime risk, mean (SD)	—	29.90 (7.90)	24.49 (4.26)	16.44 (2.61)	11.22 (4.40)
TC lifetime risk, mean (SD)	—	27.07 (4.85)	16.95 (2.29)	23.32 (2.87)	12.18 (4.12)

NOTE. Baseline demographics were defined at the index date. Because of the privacy policies of the Optum Labs Data Warehouse, sample sizes of <11 cannot be reported and appear as <11 in the table. Similarly, cells for which sample sizes of <11 could be back-calculated cannot be reported, and instead appear with > or < in the table.

Abbreviations: CRS, combined risk score; SD, standard deviation; TC, Tyrer-Cuzick.

[a]Comorbidity score was calculated on the basis of the presence of diagnosis codes on medical claims in the baseline period.

[b]Menopause stage was available for 6,840 (79.0%) patients. Denominators for the CRS+ TC+, CRS+ TC−, CRS− TC+, and CRS− TC− subcohorts were 1,957, 526, 667, and 3,690, respectively.

[c]Designation of limited family structure was available for 2,761 (31.9%) patients. Denominators for the CRS+ TC+, CRS+ TC−, CRS− TC+, and CRS− TC− subcohorts were 789, 223, 299, and 1,441, respectively.

TC− subgroups had a breast MRI, respectively. In the follow-up period, those percentages significantly increased to 19.31%, 12.64%, and 11.10% in the CRS+ TC+, CRS+ TC−, and CRS− TC+ subcohorts, respectively ($P < .001$ for all three groups; Table 2 and Fig 2). The percentage of those in the CRS− TC− subcohort receiving a breast MRI did not change

significantly in the follow-up period compared with baseline (1.24%, $P = .13$).

In the follow-up period, the three subcohorts with ≥20% lifetime risk predicted by CRS and/or TC were 11.6-23.1 times more likely to receive a breast MRI compared with the CRS− TC− group (Data Supplement, Table S4). Pairwise comparisons showed that the CRS+ TC+ subcohort was approximately twice as likely to receive a breast MRI during the follow-up period compared with the CRS+ TC− and CRS− TC+ subcohorts (Table 3).

Genetic Counseling

During the baseline period, 4.29%, 4.74%, 5.96%, and 3.61% of those in the CRS+ TC+, CRS+ TC−, CRS− TC+, and CRS− TC− subgroups received GC, respectively. In the follow-up period, those percentages significantly increased to 9.82% and 9.05% in the CRS+ TC+ and CRS+ TC− subcohorts, respectively ($P < .001$ for both groups; Table 2 and Fig 1). The percentage of patients in the CRS− TC+ and CRS− TC− subcohorts receiving GC did not significantly change in the follow-up period compared with baseline (7.13%, $P = .26$; 3.46%, $P = .66$; respectively).

In the follow-up period, the three subcohorts with ≥20% lifetime risk predicted by CRS and/or TC were 2.0-2.9 times more likely to receive GC compared with the CRS− TC− subcohort (Data Supplement, Table S5). Pairwise comparisons did not show any significant differences between the three subcohorts (Table 3).

Cancer Risk-Reduction Measures: Chemoprevention and Prophylactic Mastectomy

Among all 8,662 patients in the cohort, 38 (0.44%) were prescribed chemopreventive medication and 18 (0.21%) underwent prophylactic and/or full mastectomy during the follow-up period (data not shown). Sample sizes were too small to report results within each subcohort. Additionally, because patients with cancer prevention measures during the baseline period, including chemoprevention prescription and mastectomy, were excluded from analyses, it was not possible to compare the rates of chemoprevention or mastectomy in the follow-up and baseline periods.

DISCUSSION

PRSs have become clinically available only recently, and little is known about whether and how they guide patient care. Here, claims data revealed that patients with ≥20% lifetime risk for BC predicted by either CRS or TC were more likely to undergo enhanced management. By contrast, patients with predicted lifetime risk <20% did not appear to undertake enhanced management. These findings suggest that clinicians considered the CRS results in patient care.

To our knowledge, this study is the first to report the results of real-world, contemporary, large-scale clinical implementation of a CRS. Previous studies have mostly focused on examining clinician attitudes and hypothetical management,[29-32] and have largely found support for the notion that those with high risk predicted by a CRS/PRS are appropriate candidates for enhanced management. In a recent survey study, more than 90% of primary care physicians reported that they would use high-risk PRS results to recommend earlier or more intensive screening procedures, preventive medications, and lifestyle modifications.[29] In another survey among UK-based general practitioners, more than three quarters agreed that patients with PRS-predicted high risk of BC should be offered earlier and more frequent screening.[30] Our results are consistent with these studies; in patients with ≥20% lifetime risk predicted by the CRS, SMs increased 1.6- to 2.2-fold and MRIs increased 4.7- to 5.6-fold in the year following receipt of CRS results. A recently launched prospective study is testing similar outcomes among patients who are randomly assigned to two models of pretest education before being offered a BC CRS.[31] The results of that study will reveal whether patients who are receiving consistent, protocol-driven management recommendations undertake screening that aligns with their CRS-predicted risk. In addition, the Electronic Medical Records and Genomics (eMERGE) Network has undertaken a project to return PRS-integrated risk results to study participants, including developing guidance on how to report results that are understandable to patients.[32]

In previous studies, clinicians were less supportive of delaying or discontinuing screening when CRS/PRS results estimated low risk.[29,30] Our study appears to demonstrate this hesitancy; patients with a CRS− TC+ result had nearly the same fold-increases in SMs and MRIs (1.6-fold and 4.7-fold, respectively) as those with a CRS+ TC+ result (1.6-fold and 5.6-fold, respectively), suggesting that clinicians' actions were consistent with the TC-predicted high risk result, even when CRS predicted average risk. Later and less frequent BC screening in those with low CRS/PRS-predicted risk is being studied in the WISDOM trial[33] but likely will not be widely accepted until well-controlled, long-term studies provide strong evidence of safety.

PRSs incorporated into clinical risk prediction models enable more accurate BC risk stratification.[13,14,17-20,34-39] For example, the PRS portion of the CRS used in this study significantly improved risk prediction over the TC model alone,[15] and the CRS (PRS and TC model combined) improved predictive accuracy approximately two-fold over TC alone.[20] A UK modeling study estimated that annual mammography for 40- to 49-year-old women in the top 20% of PRS-predicted risk would reduce cancer-specific death by 14.7% versus 7.9% among a randomly selected 20% of women.[40] Here, we found that nearly 13% of individuals with TC-predicted average risk (TC−) had high CRS-predicted risk (CRS+). Without the CRS result, these high-risk individuals may not

TABLE 2. Patient Management by Subcohort in Baseline and Follow-Up Periods

	CRS+ TC+ (n = 2,423)				CRS+ TC− (n = 696)				CRS− TC+ (n = 856)				CRS− TC− (n = 4,687)			
Management Measure	Baseline	Follow-Up	Fold Change	*P*[a]	Baseline	Follow-Up	Fold Change	*P*[a]	Baseline	Follow-Up	Fold Change	*P*[a]	Baseline	Follow-Up	Fold Change	*P*[a]
SM age <40 years,[b] No. (%)	127 (11.89)	198 (18.54)	1.6	**<.001**	19 (7.69)	41 (16.60)	2.2	**.003**	32 (8.84)	52 (14.36)	1.6	**.017**	56 (4.99)	49 (4.37)	0.88	.46
Breast MRI, No. (%)	83 (3.43)	468 (19.31)	5.6	**<.001**	18 (2.59)	88 (12.64)	4.9	**<.001**	20 (2.34)	95 (11.10)	4.7	**<.001**	44 (0.94)	58 (1.24)	1.32	.13
GC, No. (%)	104 (4.29)	238 (9.82)	2.3	**<.001**	33 (4.74)	63 (9.05)	1.9	**<.001**	51 (5.96)	61 (7.13)	1.2	.26	169 (3.61)	162 (3.46)	0.96	.66

Abbreviations: CRS, combined risk score; SM, screening mammography; MRI, magnetic resonance imaging; GC, genetic counseling; TC, Tyrer-Cuzick.

[a]*P* values computed using McNemar's test; values in bold indicate $P < .05$.

[b]Denominators for patients age <40 years in the CRS+ TC+, CRS+ TC−, CRS− TC+, and CRS− TC− subcohorts were 1,068, 247, 362, and 1,122, respectively.

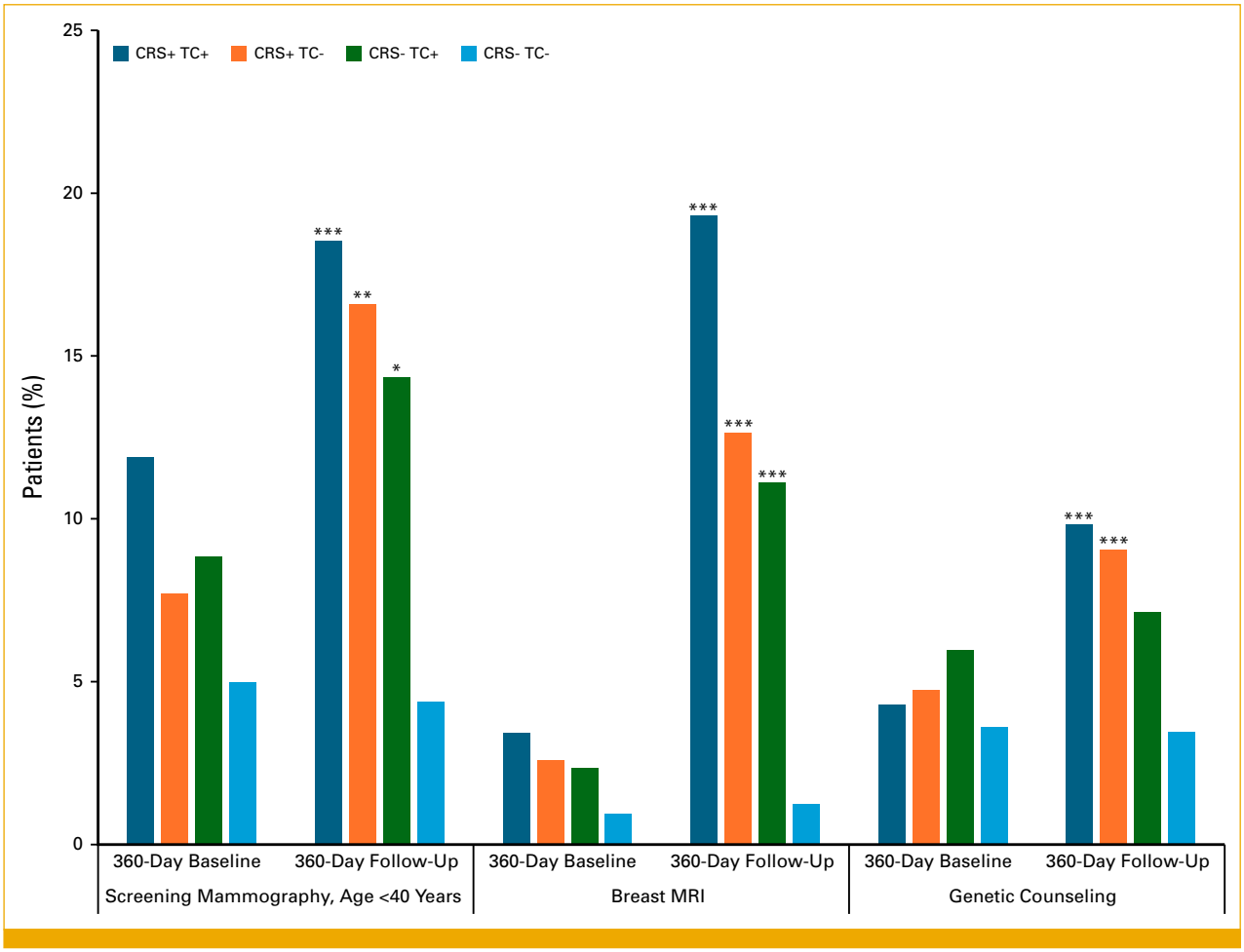

FIG 2. Proportion of patients in each subcohort receiving SM (in those <40 years), breast MRI, and GC in the baseline and follow-up periods. Dark blue: CRS+ TC+, orange: CRS+ TC−, green: CRS− TC+, light blue: CRS− TC−. *P* values are relative to the baseline measure. **P* < .05, ***P* <.005, ****P* <.001. CRS, combined risk score; GC, genetic counseling; MRI, magnetic resonance imaging; SM, screening mammography; TC, Tyrer-Cuzick.

have known they were candidates for enhanced screening. To demonstrate improved outcomes that may arise from CRS/PRS-incorporated risk stratification, additional studies are needed in prospective cohorts that compare currently recommended screening programs with those that include a CRS or PRS component.

Guidelines recommend that patients at high risk of BC be offered risk-reducing medication. Patient uptake of risk-reducing medications has been low,[41-43] with only approximately 16% of eligible patients using these medications and approximately one quarter of primary care physicians ever having prescribed them.[44] The GENRE study found that risk stratification that included a PRS influenced the use of risk-reducing medication.[45,46] We did not observe a similar trend in uptake; <1% of all patients had evidence of a prescription fill for a risk-reducing medication, yet approximately 45% were candidates on the basis of their CRS and/or TC scores. This difference may reflect real-world practice versus a controlled trial setting. Clinicians may consider medication a higher-risk intervention with potential side effects and thus be more hesitant to offer it than SM or MRI.

Guidelines do not recommend consideration of prophylactic mastectomy unless risk approaches that conferred by pathogenic variants in high-penetrance genes.[22] Additionally, the American College of Medical Genetics and Genomics advises that evidence supporting prophylactic surgery in the setting of high cancer risk should not be extrapolated to PRS-estimated risk.[47] Only 0.21% of this study's cohort had a mastectomy after receiving CRS results, suggesting that such results did not lead to inappropriate surgical management.

Strengths of this study include its large sample size, analysis of management in a real-world, contemporary setting, detailed CRS results, and the accuracy of claims data in capturing procedures. However, limitations should be noted. First, the study cohort did not reflect the racial/ethnic diversity of the US population as the CRS was not validated for individuals of non-European descent for much of the study

TABLE 3. ORs of Patient Management in 360-Day Follow-Up Period

Management Measure		CRS+ TC+	CRS+ TC−	CRS− TC+
SM, age <40 years				
Reference	CRS+ TC−	1.15 (0.71-1.87)	—	—
	CRS− TC+	1.37 (0.88-2.11)	1.19 (0.66-2.14)	—
	CRS− TC−	**5.19[a] (3.32-8.12)**	**4.52[a] (2.50-8.15)**	**3.80[a] (2.18-6.62)**
Breast MRI				
Reference	CRS+ TC−	**1.82[a] (1.31-2.53)**	—	—
	CRS− TC+	**2.00[a] (1.46-2.74)**	1.10 (0.73-1.66)	—
	CRS− TC−	**23.09[a] (15.72-33.93)**	**12.70[a] (8.05-20.04)**	**11.55[a] (7.33-18.21)**
GC				
Reference	CRS+ TC−	1.06 (0.72-1.56)	—	—
	CRS− TC+	1.44 (0.98-2.11)	1.35 (0.83-2.19)	—
	CRS− TC−	**2.91[a] (2.18-3.89)**	**2.7[a] (1.83-4.10)**	**2.03[a] (1.35-3.06)**

NOTE. ORs adjusted for covariates as noted in Methods. Significant *P* values are shown in bold.
Abbreviations: CRS, combined risk score; GC, genetic counseling; MRI, magnetic resonance imaging; OR, odds ratio; SM, screening mammography; TC, Tyrer-Cuzick.
[a]Tukey-adjusted *P* value <.05.

period. Second, analysis of management and outcomes over a longer follow-up period is necessary to demonstrate the clinical utility of CRS/PRS. Third, patients met the criteria for hereditary cancer testing and were therefore at higher cancer risk than the general population. In addition, patients were covered by commercial insurance or Medicare Advantage, which may have influenced management decisions. Fourth, a control group that did not receive CRS results was not included, so we cannot be sure that management changes were due to CRS results. Finally, because both CRS and TC results were reported to ordering clinicians, we cannot determine the extent to which one result or the other influenced management decisions; in addition, the sample sizes of the CRS+ TC− and CRS− TC+ subgroups were too small to enable meaningful comparisons of management between the two. Future studies should be conducted (1) in a population that mirrors the racial/ethnic and socioeconomic diversity of patients in the United States, (2) that follow patients for several years to assess long-term outcomes, (3) that include a control group for comparison, and (4) that directly examine the influence of each risk score on patient management.

This study demonstrated that, in alignment with guidelines, patients categorized as having a ≥20% lifetime risk of BC were more likely to receive enhanced management compared with those with <20% lifetime risk. Furthermore, clinicians appeared to manage patients on the basis of risk predicted by the CRS. CRS's ability to improve risk stratification, as well as its apparent influence on patient management, may lead to screening tailored to individual risk levels.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from Optum but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Certain data are, however, available from the authors upon reasonable request and with permission of Optum and Myriad Genetics, Inc.

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