

Uptake of polygenic risk information among women at increased risk of breast cancer

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Abstract

Polygenic risk scores (PRSs) are increasingly being implemented to assess breast cancer risk. This study aimed to assess and determine factors associated with uptake of PRS among women at increased risk of breast cancer for whom genetic testing to date had been uninformative. Participants were recruited from the Variants in Practice study from which breast cancer PRS had been calculated. Four hundred women were notified by letter of the availability of their PRS and invited to complete a self-administered survey comprising several validated scales. Considering non-participants, uptake of PRS was between 61.8% and 42.1%. Multivariate logistic regression identified that women were more likely to receive their PRS if they reported greater benefits (odds ratio [OR] = 1.17, $P = .011$) and fewer barriers to receiving their PRS (OR = 0.80, $P = .007$), had completed higher level education (OR = 3.32, $P = .004$), and did not have daughters (0.29, $P = .006$). Uptake of breast cancer PRS varied according to several testing- and patient-related factors. Knowledge of these factors will facilitate the implementation of polygenic testing in clinical practice and support informed decision making by patients.

KEYWORDS

breast cancer, polygenic risk, psychosocial, single nucleotide polymorphism, uptake

1 | INTRODUCTION

It is estimated that in addition to monogenic causes, a further 18% of the familial contribution to breast cancer can be explained by polygenic factors.¹ When the cumulative effect of common genomic variants is summarized into a polygenic risk score (PRS), studies have found that women in the highest quartile of polygenic distribution have at least a twofold increased risk for the disease compared to those with a PRS in the lowest quartile.²⁻⁴ In the familial cancer setting, polygenic information can be used to subdivide the group of women with uninformative genetic testing results for monogenic causes with regard to their ongoing breast cancer risk or the risk of contralateral disease for women previously affected.³ Based on this, and a perception of increased consumer demand for information to assist in cancer risk management, implementation of polygenic testing has begun with several commercial laboratories now offering the test.^{5,6}

Despite commercial availability, there is limited data reporting on the implementation of polygenic breast cancer risk information and uptake of the test. Prior studies have been limited to hypothetical scenarios or based on single SNP testing.⁷⁻¹¹ These studies have reported a high interest in SNP testing, with interest ranging from 74% to 80%.⁷⁻¹⁰ Interest in SNP testing was more consistently related to psychological factors (ie, perceived risk and greater cancer worry), rather than sociodemographic variables,⁷⁻¹¹ and in one study, interest was reduced among women with more negative views of the test.¹¹ It is well documented that interest in genetic testing is often higher than actual testing uptake,¹² thus these findings need to be considered with caution. Nevertheless, these studies provide the foundation to understanding decisions to pursue polygenic risk information.

Much can be learnt from the literature on *BRCA1/2* testing decisions. Studies have consistently reported that women who have higher cancer-specific anxiety are more likely to undergo *BRCA1/2* genetic testing.^{13,14} It has also been reported that women are more likely to seek out genetic testing if they have a greater need for certainty and lower tolerance for uncertainty.^{15,16} Additional qualitative studies have reported that women at high risk for breast cancer undergo *BRCA1/2* genetic testing due to a sense of responsibility toward their family, particularly female relatives in younger generations.¹⁷⁻²¹ Regarding barriers to genetic testing, women have described financial concerns,¹⁴ fear of work and insurance discrimination,^{14,18,20} practical concerns such as difficulty taking time off from family and work obligations to attend the genetic counseling appointment, and lack of access to genetics services.^{14,18,21}

It is likely that polygenic information will soon be implemented in familial cancer clinics (FCC) as a second-tier testing for women clinically assessed at increased risk for breast cancer where testing for monogenic causes has been uninformative.³ Understanding genetic testing decisions among this group of women is key to guiding the implementation of polygenic testing in clinical practice. The aim of this study was to examine uptake of breast cancer polygenic information, and determine factors associated with uptake among women from breast cancer families with uninformative genetic testing results. We hypothesized that women who have a more negative attitude toward

uncertainty, have daughters, and have higher breast-cancer-specific anxiety would be more likely to elect to receive their polygenic breast cancer information. This study was conducted as part of a prospective cohort study, which aims to assess the impact of offering polygenic breast cancer information to women at increased risk for the disease.²²

2 | METHODS

2.1 | Study design and participants

The study protocol has been described elsewhere.²² Participants were recruited from an established cohort, the Variants in Practice (ViP) study.²³ The ViP cohort is made up of women affected by breast cancer and their unaffected relatives. Prior to enrollment in the ViP study, all families had undergone a clinical assessment, genetic counseling and genetic testing at an FCC in the Australian states of Victoria and Tasmania. Additional genotyping of 62 breast-cancer-associated SNPs was conducted through the ViP study, from which an individual PRS and relative risk (RR) for breast cancer were generated.²⁴

Additional eligibility criteria for this study included: women aged ≥ 18 years who had received uninformative genetic testing results of high- and moderate-risk breast cancer genes. No exclusions were made based on personal history of breast cancer. This study was approved by the Peter MacCallum Cancer Centre (HREC/16/PMCC/2) and the Tasmanian Research Ethics Committee (H0016395).

2.2 | Recruitment and data collection

Women meeting these criteria were mailed the study information and consent form, an educational pamphlet describing polygenic breast cancer risk (Supplementary material 1),²⁵ and a response sheet. Those who opted into the study completed a baseline questionnaire (Q1). The study information sheet notified individuals that they would be eligible to enroll in the study regardless of their decision to receive their PRS; thus both women who wished to receive their PRS and those declining this offer were eligible to participate. Reminder letters and phone calls were made to participants who did not return the study response sheet and who failed to complete Q1 as required.

Participants who indicated intention to receive their PRS in Q1 were contacted by the study team and an appointment was booked at one of the six participating FCCs located in the Australian states of Victoria and Tasmania. Participants who failed to attend three appointments without contacting the FCC were categorized as a "decliner."

2.3 | Disclosure of PRS

Participants received their PRS by attending an in-person appointment with a qualified genetic health professional (eg, genetic

counselor, clinical geneticist, or oncologist with training in familial cancer). The appointments included disclosure of the participant's personalized breast cancer PRS, a discussion about the implications of their PRS in line with participants' personal and/or family history of breast cancer, and breast cancer risk management strategies. A graphical representation of participants' PRS, including their RR of breast cancer compared to the Australian general population and the impact of lifestyle factors (alcohol consumption and body mass index greater than 30) were used when explaining PRS results.²⁴

2.4 | Measures

Clinical characteristics such as personal breast cancer history and number of affected relatives were available through the VIP database.²³ The baseline survey elicited the following data:

Demographic characteristics—sociodemographic data included age, country of origin, marital status, educational level, language spoken at home, children (including number of daughters), and previous attendance at an FCC.

Intention to receive PRS—participants were asked whether they would like to receive their PRS with three response options: “Yes, and please contact me to arrange an appointment,” “No, and do not contact me to arrange an appointment,” and “Unsure, I would like more information before making this decision. Please contact me to discuss this further.”

Perceived severity of breast cancer was assessed with one item. Participants were asked to rate the severity of breast cancer from “not serious at all” (1) to “extremely serious” (5).²⁶

Perceived breast cancer risk—Participants were asked to rate their own breast cancer risk relative to an average person the same age and gender, and a person with a similar family history of breast cancer using a scale from “much lower” (1) to “much higher” (5). Participants also self-rated their chances of developing breast cancer in the future using a visual analogue scale from “no chance” (0%) to “certainly will develop breast cancer” (100%).²⁶

Perceived benefits—eight items were adapted from Kasparian et al²⁶ to assess perceived benefits of receiving one's PRS (eg, learn about my children's risk). Scores range from 0 to 24, with higher scores indicating higher perceived benefits of the test (Cronbach's alpha = .71).

Perceived barriers—seven items were adapted from Kasparian et al²⁶ to assess perceived barriers to receiving one's PRS (eg, concern about the impact of genetic information on my family). Scores range from 0 to 21, with higher scores indicating higher perceived barriers to receiving their PRS (Cronbach's alpha = .82).

Self-efficacy—seven items were adapted from Fisher et al²⁷ to assess confidence in receiving one's PRS despite “obstacles.” Scores range from 7 to 35, with higher scores indicating higher ability to access the test (Cronbach's alpha = .78).

Uncertainty avoidance was assessed using the 8-item Attitudes Towards Uncertainty scale.¹⁵ Total scores range from 1 to 5, with higher scores indicating a more negative attitude toward uncertainty (Cronbach's alpha = .81).

Knowledge of familial breast cancer and polygenic risk—10 true-false items were adapted from Erlich et al²⁸ and Ondrusek et al²⁹ to assess knowledge of hereditary breast cancer and polygenic risk. A total score was calculated by summing the total number of correct answers (range 0-10), with higher scores indicating more knowledge of familial breast cancer (Cronbach's alpha = .63). Self-reported knowledge of polygenic risk was also assessed, with participants asked to rate how much information they had read about the common risk variants used to assess breast cancer risk with responses ranging from “nothing” to “a lot of information.”

Breast cancer anxiety was measured using the Impact of Events Scale (IES), a measure of intrusion and avoidance toward a stressor, in this case being at risk for breast cancer.³⁰ A total score was obtained by summing the items (range 0-75), with a higher score indicating more breast cancer anxiety (Cronbach's alpha = .94).

General anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS). A total scale score was obtained by summing each item (range 0-42), with a higher score indicating more general anxiety and depression (Cronbach's alpha = .86).

Stressful life events was assessed using the 12-item List of Threatening Experiences, which measures common threatening life experiences, including serious illness and death in the family.³¹ Threatening life events may affect anxiety and distress levels and were measured as a potential confounding variable.

2.5 | Statistical analysis

Data were analyzed using SPSS 25. Descriptive statistics were used to describe the sociodemographic, clinical, and psychological characteristics of the sample. Univariate logistic regression was conducted between predictor variables and uptake of PRS. Variables that had significance levels of $P < .25$ in the univariate analysis were included in the multivariate regression model. Logistic regression analysis was then employed to identify variables that were independently associated with uptake of PRS using a backwards elimination strategy until only those with P -values of $< .05$ were included in the final model. Stressful life events and demographic measures, including previous FCC attendance, were included as potential confounding variables. Model fit was assessed using the Hosmer-Lemeshow goodness of fit test.

3 | RESULTS

3.1 | Response rate and participation bias

Recruitment occurred from August 2016 until August 2018. Of the 400 women invited to the study, 8 were deceased, 217 consented to participate and 208 completed the baseline questionnaire, yielding a participation rate of 53.1%. Demographic and clinical characteristics of participants are shown in Table 1. The mean age of participants at baseline was 52.3 years (SD = 13.1), the majority were born in

Australia (87.4%) and spoke English at home (97.1%). Approximately half of the participants had a personal history of breast cancer ($n = 106$, 51.0%). Most participants had previously attended an FCC to discuss their personal and/or family history of breast cancer ($n = 124$, 59.9%), with 97 (46.6%) having personally undergone *BRCA1/2* genetic testing for which results were uninformative. Among affected women the mean age of their first breast cancer diagnosis was 45.1 years (range: 24-75 years).

As per the study protocol, reminder letters and phone calls were made to participants who did not return the study invitation letter. Out of the 184 women who did not participate in the study, only

59 (32.1%) declined to participate, either by returning the study invitation letter or upon follow-up contact. The remaining 124 participants could not be contacted, and it is not known if these individuals received the study invitation letter or if they were not interested in participating in the study.

Of the 184 nonparticipants, 105 (57.1%) had a personal history of breast cancer and 93 (50.5%) had personally undergone *BRCA1/2* genetic testing and received uninformative results (Table 2). Participants and nonparticipants did not differ by age, personal history of breast cancer, number of affected relatives, and whether they had previously undergone *BRCA1/2* genetic testing (Table 2).

TABLE 1 Demographic and clinical characteristics for PRS receivers, decliners, and the total sample ($n = 208$)

Variable	Level	Receivers, n (%)	Decliners, n (%)	Total sample, n (%)
Age (y)	18-29	6 (3.7)	2 (4.7)	8 (3.9)
	30-39	25 (15.5)	3 (7.0)	28 (13.6)
	40-49	44 (27.3)	10 (23.3)	54 (26.2)
	50-59	42 (25.8)	15 (34.9)	57 (27.7)
	60-69	33 (20.5)	6 (14.0)	39 (18.9)
	>70	13 (8.1)	7 (16.3)	20 (9.7)
Has daughters	No	77(46.7)	11 (25.6)	88 (42.3)
	Yes	88 (53.3)	32 (74.4)	120 (57.7)
Employment status	Employed	110 (66.5)	26 (60.4)	136 (66.0)
	Unemployed	23 (14.1)	6 (14.0)	28 (13.6)
	Retired	30 (18.4)	11 (25.6)	42 (20.4)
Occupation health care professional	No	142 (87.1)	36 (85.7)	174 (85.3)
	Yes	20 (12.3)	6 (14.3)	30 (14.7)
Marital status	Single	55 (33.5)	10 (23.3)	65 (31.4)
	Married/de facto	109 (66.5)	33 (76.7)	142 (68.6)
Education level	High school and below	29 (17.7)	13 (30.2)	42 (20.3)
	Certificate	39 (23.8)	16 (37.2)	55 (26.6)
	Bachelor and above	96 (58.5)	14 (32.6)	110 (53.1)
Birthplace	Australia	142 (86.6)	39 (90.7)	181 (87.4)
	Other	22 (13.4)	4 (9.3)	26 (12.6)
Language spoken at home	English	159 (97.5)	41 (95.3)	200 (97.1)
	Other	4 (2.5)	2 (4.7)	6 (2.9)
Breast cancer history	Affected	84 (50.9)	22 (51.2)	106 (51.0)
	Unaffected	81 (49.1)	21 (48.8)	102 (49.0)
Total number of FDR and SDR diagnosed with breast cancer	0	25 (15.2)	7 (16.3)	31 (15.0)
	1	40 (24.4)	16 (37.2)	63 (30.4)
	2	56 (34.2)	9 (20.9)	64 (30.9)
	3+	43 (26.2)	11 (25.6)	49 (23.8)
Attended FCC in the past	Yes	106 (64.6)	22 (51.2)	128 (61.8)
	No	44 (26.8)	19 (44.2)	63 (30.4)
	Unsure	14 (8.5)	2 (4.6)	16 (7.7)
Intention to receive PRS at baseline	Yes	158 (95.8)	22 (51.2)	180 (86.5)
	No	0 (0)	10 (23.3)	10 (4.8)
	Unsure	7 (4.3)	11 (25.6)	18 (8.7)

Abbreviation: PRS, polygenic risk score.

3.2 | Uptake of PRS

Out of the 208 participants who completed the baseline questionnaire, 180 (86.5%) indicated interest in receiving their personal PRS, 10 (4.8%) declined this offer, and 18 (8.7%) were unsure. By the time of study completion, 165 had attended an FCC and received their PRS ("receivers"), and 43 had declined this offer ("decliners"). Considering the additional 184 participants who declined to participate in the study, and hence did not complete the baseline survey or receive their results, uptake of PRS was 42.1% ($n = 165$ out of 392). However, since only 59 nonparticipants returned the study response sheet, it is not possible to exclude whether the remaining 124 non-participants received the study invitation letter known or if they were not interested in participating in the study. Thus, the true uptake of PRS for breast cancer risk in this study lies between 61.8% and 42.1%.

3.3 | Perceived benefits and barriers to receiving PRS

Figure 1 shows the percentages of participants who selected "somewhat" or "very much" for the perceived benefits and barriers to receiving their personal PRS separately for receivers and decliners. There were several differences in how receivers and decliners rated these items. For example, in nearly all cases receivers endorsed higher practical benefits to receiving their PRS when compared to decliners. Specifically, the majority of receivers endorsed the following statements as influencing their decision to receive their PRS: "get information about how to manage my risk of developing cancer" (94.5%), "be

more certain about my cancer risk" (90.3%), and "plan for the future" (86.1%). In comparison, fewer decliners rated these items as influencing their decision, 80.5%, 75.0%, and 68.3%, respectively (Figure 1).

Similarly, there were large differences in how the two groups rated the potential barriers to receiving their PRS, with decliners endorsing higher emotional barriers when compared to the receivers. For example, 52.6% of decliners reported concerns about their ability to cope with the information emotionally, whereas only 34.8% of receivers endorsed this item as a potential barrier. In comparison to receivers (15.0%), decliners also had higher fatalistic concerns about breast cancer with 34.2% of women in this group endorsing the following statement: "it wouldn't change my belief that cancer is inevitable" as somewhat or very much influencing their decision not to receive their PRS. There was only one item, "possible impact on insurance," for which endorsement was lower in the decliner group (34.2%) compared to receivers (46.6%).

3.4 | Knowledge of familial cancer and PRS

When participants were asked to rate how much information they had read on the common risk variants associated with breast cancer risk, 48.8% of decliners and 37.8% of receivers indicated they had read nothing or almost nothing. Similarly, 44.2% of decliners and 47.6% of receivers indicated they had read some information, while fewer women reported having read a fair amount or a lot of information, 7.0% and 14.6%, respectively.

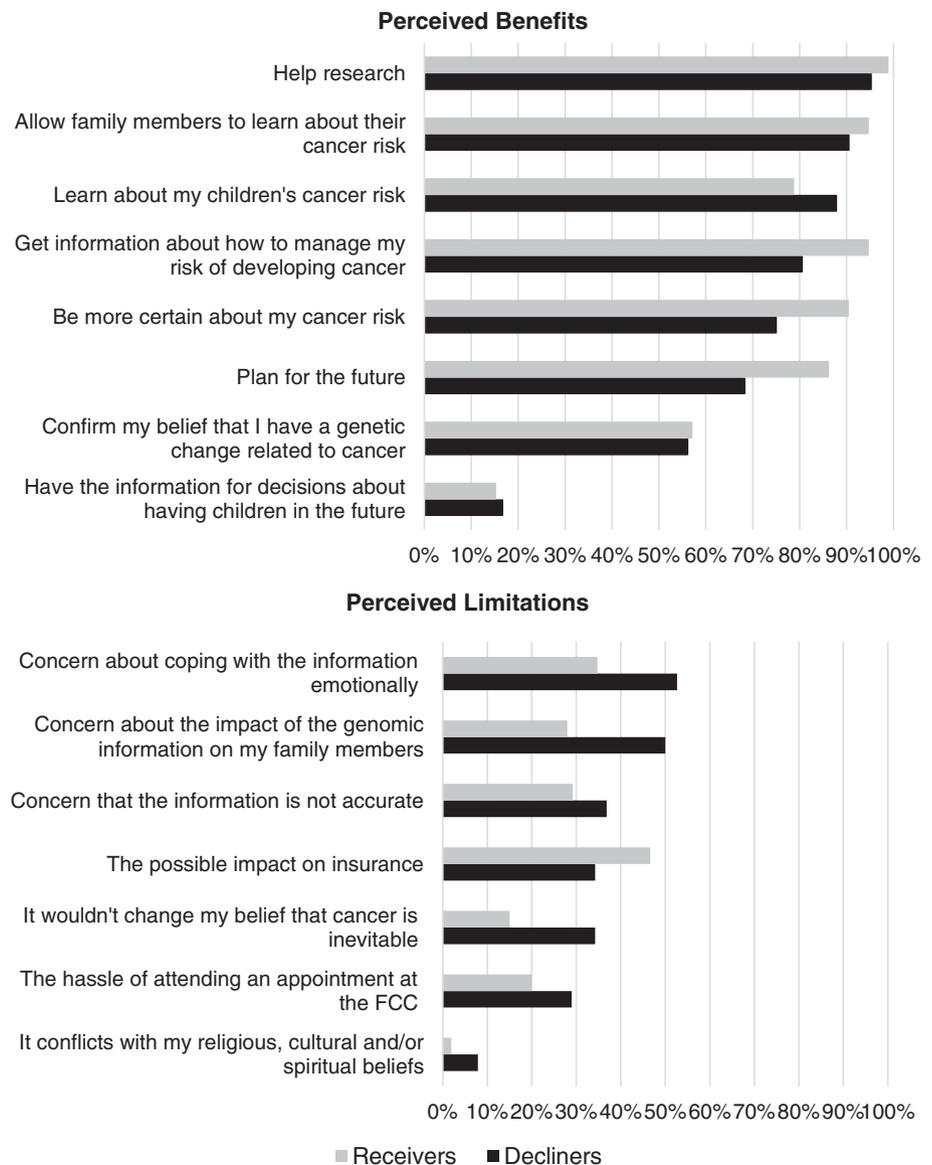
There were differences in the rate of correct answers between decliners and receivers. For example, 59.4% of women who received

TABLE 2 Demographic and clinical characteristics of study participants and nonparticipants

		Nonparticipants (excl. known deceased (8))				Test statistic		
		Consented		Nonparticipants (excl. known deceased (8))		X ²	df	P
		N	%	N	%			
Age (y) ^a	18-29	5	2.4	4	2.2	7.1	5	.21
	30-39	25	12.0	23	12.5			
	40-49	46	22.1	38	20.7			
	50-59	61	29.3	46	25.0			
	60-69	44	21.2	31	16.8			
	>70	27	13.0	42	22.8			
Phx breast/DCIS	Affected	106	51.0	105	57.1	1.5	1	.23
	Unaffected	102	49.0	79	42.9			
Total number of FDR and SDR with breast cancer or DCIS	0	31	14.9	38	20.7	2.5	3	.48
	1	67	32.2	57	31.0			
	2	61	29.3	52	28.3			
	3+	49	23.6	37	20.1			
Clinical BRCA mutation detection testing with a participating FCC?	Yes	97	46.6	93	50.5	0.6	1	.44
	No	111	53.4	91	49.5			

^aAge reported in Table 1 denotes age at time of data analysis. This is different to age reported in Table 2 which is participants' self-report age at completion of baseline survey.

FIGURE 1 Percentages of receivers and decliners endorsing perceived benefits and barriers to receiving their personal polygenic risk score (PRS) as “somewhat” or “very much” influencing their decision to receive PRS ($n = 208$)



their PRS correctly identified the following statement: “if a woman learns that she does not have a fault in the *BRCA1* or *BRCA2* genes, that means the breast cancer in her family cannot be hereditary” as false. In comparison only 29.3% of decliners correctly categorized this statement (Figure 2). Similarly, 69.1% of receivers correctly responded to: “there is more than one DNA change that can increase a woman's risk for breast cancer,” while less than half (45.2%) of decliners correctly answered this question.

3.5 | Predictors of PRS uptake

The association between the predictor variables and uptake of PRS are shown in Table 3. Model fit as assessed with Hosmer-Lemeshow goodness-of-fit test which indicated adequate fit ($P = .685$). None of the psychological measures (IES and HADS), clinical history, or having read information about common risk variants were associated with

uptake of PRS in the univariate logistic regression (Table 3). Although significant in the univariate logistic regression, uncertainty avoidance and self-efficacy were no longer statistically significant when controlling for the other predictor variables (Table 3).

After adjusting for other predictor variables and potential confounders, the multivariate logistic regression suggest uptake of PRS was significantly associated with perceiving fewer barriers to the test (OR = 0.80, 95% CI = 0.69-0.94, $P = .007$), higher perceived benefits of the test (OR = 1.17, 95% CI = 1.04-1.30, $P = .011$), not having daughters (OR = 0.29, 95% CI = 0.12-0.70, $P = .006$), and having completed bachelors education (OR = 3.32, 95% CI = 1.46-7.55, $P = .004$).

4 | DISCUSSION

To our knowledge, this is the one of the first prospective studies to explore women's decision to receive polygenic breast cancer risk

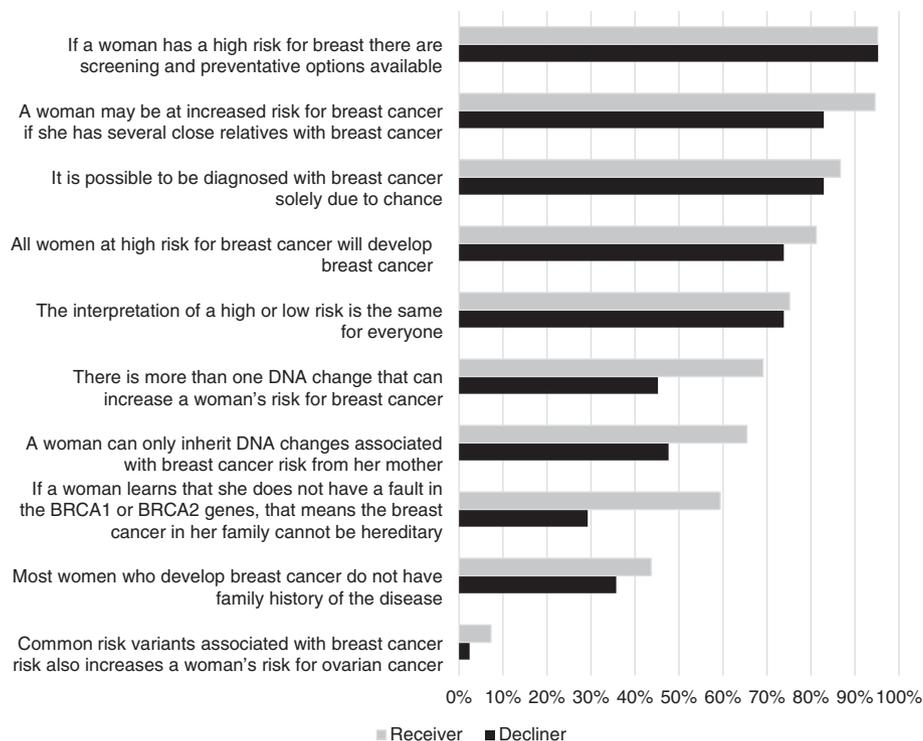


FIGURE 2 Percentage of correctly answered knowledge questions about familial breast cancer and polygenic risk by receiver and decliners

information. Our study demonstrated that women at increased risk of breast cancer for whom previous genetic testing has been uninformative are interested in accessing updated genetic information that may clarify their level of risk. Our reported uptake (61.8%-42.1%) is in line with mean uptake of *BRCA1/2* testing (59%) reported in a previous systematic review of breast cancer genetic testing decisions.³² Despite all families in this study having previously undergone *BRCA1/2* genetic testing, less than 61.8% of participants chose to receive updated genetic risk information in the form of PRS. Reasons for participants declining to receive their PRS remain unknown. However, findings from our study may have shed light on factors that may have influenced women to receive their PRS.

Previous studies into early adopters of new genetic technology such as *BRCA1/2* genetic testing³³ and whole genome sequencing³⁴ identified that these individuals were more likely to be information seekers, with higher formal education. Additionally, early adopters will seek new information in the hope to improve their understanding about disease risk and health management, and will choose to proceed with testing even if faced with uncertainty about the potential risk and usefulness of information.^{33,34} These findings are reflected among our participants, with women who received their PRS being more likely to have completed higher level education, reported greater benefits and fewer barriers to receiving their results. In contrast, women who opted not to receive their PRS were more likely to have done so due to concerns about their emotional response and in the absence of balanced medical information.

Women's self-reported perception of the benefits and barriers to receiving polygenic information was strongly associated with uptake of results. Compared to decliners, receivers reported higher practical benefits to receiving their PRS, such as planning for the future and

accessing information to manage breast cancer risk. In comparison, decliners reported higher emotional barriers such as coping with information emotionally and concerns about the impact of information on family members. These findings are consistent with studies of genetic testing decisions, with a previous systematic review identifying perceived benefits and barriers of the test as one of the strongest predictors of testing uptake.³⁵ Such findings suggest that any interventions aimed at facilitating genetic testing decisions should involve an exploration of the extent the individual believes the test will be beneficial for them, as well as concerns and potential barriers to undergoing the test.

In contrast to our hypothesis, breast cancer anxiety and attitudes toward uncertainty were not associated with uptake of polygenic breast cancer information. Similarly, clinical history such as personal history and family history of breast cancer was not associated with uptake of PRS. Unexpectedly, we also found that women without daughters were more likely to receive their personal PRS compared to those with daughters. This finding remained even when adjusted for demographic factors such as age, educational level, and marital status. It is possible to interpret this finding in light of the multivariate model, where women who declined to receive their results also reported fewer benefits and more concerns about receiving their PRS. It is possible participants with daughters declined to receive their results to "protect" their relatives as they felt the benefits to receiving this information did not outweigh the potential for negative outcomes. It is also possible that prior experiences with breast cancer, such as a death in the family or having an affected mother confounded these results. For example, women who experience a death in a close relative may have greater fatalistic beliefs about breast cancer, and this experience may have influenced their decision not to pursue additional genetic testing.

TABLE 3 Univariate and multivariate logistic regression assessing for predictors of PRS uptake

Predictor variable	Receivers N (%)	Decliners N (%)	Univariate logistic regression		Multivariate logistic regression	
			OR (95% CI)	P value	OR (95% CI)	P value
Have daughters	53.3% have daughter	74.4% have daughters	0.39 (0.19-0.82)	.015	0.29 (0.12-0.70)	.006
Have personal history of breast cancer	50.9% Yes	51.2% Yes	0.920 (0.47-1.80)	.809	—	—
Level of education	58.5% completed a bachelor's degree	32.6% completed a bachelor's degree	2.92 (1.44-5.95)	.003	3.32 (1.46-7.55)	.004
Predictor variable	Receivers mean (SD)	Decliners mean (SD)	OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Total number of FDR and SDR diagnosed with breast cancer	1.8 (1.2)	1.6 (1.2)	1.13 (0.85-1.5)	.395	—	—
Perceived severity of breast cancer	4.4 (0.79)	4.4 (0.92)	1.01 (0.67-1.55)	.931	—	—
Perceived risk	3.4 (0.8)	3.3 (0.8)	1.01 (0.67-1.55)	.931	—	—
Self-efficacy	27.1 (4.6)	24.4 (5.9)	1.11 (1.04-1.20)	.003	NS	—
Perceived benefits of the test	10.4 (3.1)	9.4 (3.8)	1.14 (1.02-1.25)	.024	1.17 (1.04-1.30)	.011
Perceived barriers to the test	2.3 (2.1)	3.0 (3.1)	0.86 (0.75-0.99)	.031	0.80 (0.69-0.94)	.007
Uncertainty	4.0 (0.6)	3.7 (0.7)	1.97 (1.1-3.3)	.012	NS	—
Knowledge	6.8 (1.8)	5.6 (2.2)	1.34 (1.12-1.59)	.001	NS	—
HADS total scale	7.8 (5.5)	7.5 (5.5)	1.1 (0.95-1.07)	.720	—	—
IES total scale	9.5 (13.9)	9.9 (14.0)	0.10 (0.97-1.10)	.867	—	—

Abbreviation: HADS, Hospital Anxiety and Depression Scale; IES, Impact of Events Scale; PRS, polygenic risk score NS, not significant.

Note: Bold value denoted the significant values are listed in the column called P value. The significant values for self-efficacy, uncertainty and knowledge were not provided as they were not significant in the multivariate logistic regression.

Our study did not permit an extensive assessment of family history and its impact on PRS uptake. Future studies should aim to further explore the association between lived experiences and uptake of PRS.

As PRS continues to be implemented in clinical practice, it is important to conduct additional studies to assess how women respond to receiving this complex information. These studies should assess women's understanding of PRS, and their psychological and behavioral outcomes. New frameworks will also need to be developed to ensure PRS are effectively communicated. Such frameworks will need to account for monogenic risk genes and other breast cancer risk factors such as family history and lifestyle. Studies assessing the different applications of PRS should also be conducted, including as a modifier of high- and moderate-risk breast cancer risk genes,^{36,37} and for population screening programs.³⁸⁻⁴⁰ Each application of PRS will have its own unique set of research questions which will need to be investigated.

Results should be interpreted in light of the study's strengths and limitations. First, this cohort was made up of a diverse group of women that included individuals with and without a personal history of breast cancer, as well those who had attended an FCC in the past and those who had not. However, nearly all women were born in Australia and spoke English at home, thus generalizability

to cultural and linguistic minorities is limited. Secondly, we reported a range of PRS (61.8% and 42.1%) based on nonparticipants. Attempts were made to ensure individuals were informed that they were eligible to participate in the study regardless of their decision to receive their PRS. Despite this, it is likely that individuals self-selected to participate based on interest in receiving their PRS, and therefore, uptake figures may not be completely representative of women offered polygenic testing. The results from our regression model should also be interpreted with caution as the number of decliners ($n = 43$) does not meet the events per predictor variable rule.⁴¹ However, we included all eligible variables in our regression model based on the theoretical framework used, and on significance level cutoffs as their inclusion is justified due to statistically significant associations.⁴² Finally, it should be noted that research is still ongoing to identify SNPs associated with breast cancer risk⁴³ and to determine the best performing PRS.^{44,45} Hence, it is possible the present PRS will need to be updated in the future. Despite these limitations, our findings point to potential areas for intervention to facilitate genetic testing decisions that include improving knowledge of familial breast cancer and PRS and exploring perceived benefits and barriers to accessing polygenic information. Additionally, our findings indicate a high interest in receiving personalized breast cancer PRS, suggesting

some women who receive uninformative genetic testing results will continue to seek information to clarify their risk level.

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CONFLICT OF INTERESTS

B.M. has a remunerated consultant role with the company Astra Zeneca with respect to an unrelated project. Astra Zeneca has not been involved in the collection or analysis of data for articles nor in writing or submitting this manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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