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Cancer patient knowledge about and behavioral intentions after germline genome sequencing

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ABSTRACT

Objectives: Germline genome sequencing (GS) is becoming mainstream in cancer diagnosis and risk management. Identifying knowledge gaps and determinants of health behavior change intentions will enable effective targeting of educational and management strategies to translate genomic findings into improved cancer outcomes.
Methods: Probands diagnosed with cancer of likely genetic origin that consented to but not yet undergone GS, and their biological relatives, completed a cross-sectional questionnaire assessing GS knowledge and hypothetical intention to change behaviors.
Results: Probands (n = 348; 57% university educated) and relatives (n = 213; 38% university educated) had moderate GS knowledge levels, with greater knowledge associated with higher education. Both populations reported high behavioral change intentions, significantly associated with being female (p = 0.01) and greater perceived importance of GS (p < 0.001), and for probands: being from English-speaking households (p = 0.003), higher socio-economic status (p = 0.01) and greater self-efficacy (p = 0.02).
Conclusions: Increasing GS knowledge will enable realistic participant expectations surrounding germline GS. Actual behavior change should be monitored to determine whether increased cancer risk knowledge results in altered cancer-related behavior and ultimately, cancer outcomes.
Practice implications: Educational resources should target specific populations to ensure informed decision-making and expectation management. Support tools facilitating and maintaining behavioral change may be needed to achieve improved cancer patient outcomes.

1. Introduction

Genome sequencing (GS) is increasingly being used to identify hereditary genetic drivers of disease, and to inform clinical management [1]. In cancer, germline genetic testing has focused on single gene testing or small gene panels associated with specific cancer types, exemplified by *BRCA1/2* in breast cancer patients and mismatch repair genes in colorectal cancer patients [2,3]. Sequencing technology cost has significantly declined, making GS more accessible. Consequently, germline and somatic tumor GS have expanded to include hundreds of genes to guide cancer treatment, prognosis and risk management including prevention and surveillance [4,5]. However, the amount and complexity of genomic

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information provided by more extensive testing makes it difficult to fully understand.

As GS becomes mainstream, it is important to assess patients' knowledge of germline GS, and whether they intend to act on results. Adequate knowledge about the benefits and limitations of GS ensures that patients have realistic expectations, as demonstrated by a previous study showing that patients undergoing genetic counselling that utilized a website providing cancer-specific information had less unrealistic expectations about genetic testing [6]. Knowledge of germline GS may also provide patients with greater confidence in their ability to cope with receiving test results, temper disappointment, lessen anxiety/distress and support decision-making [7,8]. Finally, expansive GS will only yield expected benefits if participants use results to guide risk reduction, early detection and cancer prevention behaviors [9].

Genomic knowledge varies considerably, depending on the patient population and method of knowledge assessment, patients' level of education and previous attendance at a family cancer clinic (FCC) [8,10,11]. Participants in previous studies included those who are healthy seeking disease risk information, and those with rare disorders undergoing GS to guide treatment. A recent systematic review of knowledge of genomics in cancer patient populations revealed limited knowledge and high need for education [12]. This concurs with the broader literature on genetics, where key issues are often poorly understood by patients [13–15].

Factors associated with poorer knowledge included rural residence, older age, minority status, and lower education, as well as low numeracy and literacy [16]. Few studies have examined psychological factors associated with knowledge of genomics. Health behavior models suggest that those with high perceived susceptibility to disease are more likely to act to prevent that disease, and that the decision to act is reached through a deliberate reasoning process or analysis of susceptibility, potential actions, potential costs, and anticipated outcomes [17]. Thus, those with higher perceived susceptibility may be more motivated to seek out and understand information to support this decision-making.

One study examined associations between self-efficacy, perceived susceptibility, attitude toward uncertainty and satisfaction with the decision to have testing, and knowledge of tumor mutation profiling in advanced cancer patients [18]. The authors found a significant association only for satisfaction with decision. However, how these results generalize to patients affected by rare and less common cancers undergoing GS to determine future cancer risk is unknown.

Overall, the evidence that genomic information will influence behavior is lacking [19]. Most studies of lower-risk genotypes have evaluated genetic feedback based on single-gene variants, revealing little behavioral impact, either positive or negative [20]. A systematic review and meta-analysis of trials delivering personalized DNA-based estimates of disease risk to the general public for single conditions where risk could be reduced by behavior change, found no evidence of impacts on diverse behaviors such as smoking cessation, diet or physical activity, although the authors noted the overall poor quality of studies [21].

Receiving genomic results has, however, been shown to encourage more frequent health screening, altered lifestyle behaviors and other preventative strategies in healthy adults [22], if the results are linked to known effective prevention strategies [23,24] and if the risks are high. For example, participants in one study were more motivated to limit sun exposure and increase screening after they received melanoma risk information based on family history and genetic results (*CDKN2A* mutation positive) versus family history alone [25]. However, the extent to which these results generalize to a population who have already experienced cancer, is unknown. Behavioral outcomes of risk feedback based on testing for numerous gene variants simultaneously remain largely unexplored.

Furthermore, most studies have measured intent to, rather than actual, change following receipt of genomic results, reflecting the difficulty and greater cost of longitudinal studies. The intention-behavior gap (the failure to translate intentions into action) is well documented; data suggest that intention predicts a mere 30–40% of variation in health behavior [26]. However, knowledge of the determinants and strategies that facilitate translation of intention to behavior is increasing [27].

Few of the above studies were informed by theory. Protection Motivation Theory (PMT) postulates that individuals shield themselves from threats based on the perceived efficacy of preventive behavior and self-efficacy of performing the preventive behavior [28]. Accordingly, individuals' perception of the degree of personal threat posed by cancer, GS knowledge, and perceptions of the efficacy of GS in guiding preventive management, and self-efficacy for undertaking preventive behaviors, will impact their intentions to undertake such behaviors.

Notably, a negative attitude toward uncertainty has been found to increase threat appraisal [29]. Furthermore, Brouwers and Sorrentino showed that attitude toward uncertainty provides greater predictive power when combined with PMT, to explain individuals' responses to increasing threat [30]. The authors argue that people with a negative attitude toward uncertainty are more motivated to see information and ways to resolve uncertainty, particularly under conditions of increasing threat. Yet these variables have rarely been explored in relation to intention to undertake preventive behaviors following GS.

The current study aimed to address gaps in the literature identified above by investigating baseline knowledge and determinants of behavioral change intention in patients undergoing germline GS. Our goal was to help health professionals to more effectively target future educational and management strategies that will translate genomic findings into improved health outcomes.

The Genetic Cancer Risk in the Young (RisC) study is a cohort study of participants with a personal history of cancer, investigating heritable cancer causes and future cancer risk using germline GS. A psychosocial substudy of RisC (Psychosocial Issues in Genomic Oncology - PiGeOn) [31] is exploring psychosocial and behavioral outcomes in RisC participants. Using baseline quantitative data from the PiGeOn study, the study hypothesis was that:

Controlling for demographic and cancer-related variables that may impact the outcomes, PMT variables (greater perceived cancer susceptibility, perceived importance of GS, and self-efficacy); higher levels of satisfaction with the decision to have GS (as a result of more realistic expectations of GS); and more negative attitudes toward uncertainty would be associated with greater GS knowledge and behavioral intentions.

2. Methods

2.1. Participants and study design

Participants were recruited from the RisC study, which recruits adults with a likely genetic predisposition to cancer: a cancer diagnosis between 16 and 40 years of age, or two cancer diagnoses at < 50 years of age, or three separate cancer diagnoses at any age (probands). RisC participants are recruited by clinical cancer geneticists, genetic counselors and oncologists, or self-referral. While gaining consent, a researcher provides participants with written information about germline GS and the study, offered participants the opportunity to ask questions and gives contact information for study personnel if questions arose in due course. Participants provide a blood sample from which DNA is extracted and germline GS performed. If pathogenic variant(s) are found in the current clinically actionable American College of Medical Genetics reportable gene list, participants are referred to a familial cancer clinic or other

appropriate clinical service and offered tailored risk management plans. Biological relatives, often parents, are also invited to enroll in the RisC study. Participants receive GS results approximately 18 months after consent.

When consenting to the RisC study, participants also consent to the PiGeOn psychosocial study [31]. PiGeOn participants complete three questionnaires, administered at consent (baseline), and three months and one year after consent. Participants are reminded by phone and/or email if questionnaires are not received within three weeks of sending. The current paper reports baseline quantitative results examining demographic, disease and psychological predictors of GS knowledge and intended behavioral change at baseline.

All participants in the RisC study provided written, informed consent. Human ethics approval was obtained from Human Research Ethics Committees at St Vincent's Hospital, Sydney, Australia (HREC/16/SVH/24).

2.2. Measures

Probands and their relatives completed an identical questionnaire, including validated scales where available and purpose-designed questions as appropriate.

2.2.1. Demographic variables

Participant demographics included: gender, age, education, occupation, language spoken at home used as a determinant of a culturally and linguistically diverse background, postcode (for socioeconomic status [SES] and remoteness [Accessibility and Remoteness Index of Australia]), and marital and parental status. An occupation was designated a medical/science occupation if the education toward or the occupation itself involved scientific learning or evidence-based medical practice (e.g. research scientists, registered medical practitioners, allied health professionals). Classifications were made by one member of the research team and cross-checked by another.

2.2.2. Cancer variables

Personal and family history of cancer, previous attendance at an FCC, time since (first) cancer diagnosis, and cancer type(s) were collected.

Demographic and cancer variables were assessed to ensure variables that might impact knowledge and behavioral intention (such as greater exposure to information and resources in an urban center, and through education) were controlled for in the analysis.

2.2.3. Knowledge of genomics

We developed a seven-item study-specific knowledge scale (questions listed in Fig. 3). The only validated knowledge scale relevant to GS published at the time of study inception [32] was validated on ClinSeq participants who had consented to undergo GS as part of a long term research study. As a knowledge scale relevant to the benefits and limitations of GS for cancer risk was not available, a study-specific scale was developed. A multi-disciplinary advisory group comprising geneticists, genetic counsellors, genomic scientists and psycho-oncologists nominated issues they felt were critical for participants to understand to have realistic expectations of test outcomes. Items addressed aspects such as the likelihood of obtaining informative results, cancers in which informative results are more likely to be found, and availability of tailored risk-management or treatment options. Items were multiple choice and included a '*Don't know*' option. Following a pilot with ten participants, slight modifications to wording were made to increase the clarity of items. Further piloting with another ten participants confirmed the scale had face validity and was understandable. A total score (0–100%) was calculated from the number of correct responses, with '*Don't know*' responses scored as incorrect. Knowledge scores were divided into quartiles; the lowest quartile was categorized as 'low', the middle two quartiles as 'moderate', and the upper quartile as 'high'.

2.2.4. Behavioral intentions

Participants completed a study-developed measure based on the literature, assessing intention to change six behaviors (diet, exercise, alcohol consumption information seeking, health screening and stress management) if they had a known gene variant that increased their cancer risk (Appendix A). Items were rated on a 5-point Likert scale from '*Strongly disagree*' (1) to '*Strongly agree*' (5) and averaged (Cronbach's alpha 0.89). Higher scores indicate greater intention to change behavior. Average scores above 4.0 were labeled as 'high'.

2.2.5. Perceived importance of GS

Five items asked participants to rate importance of GS, with higher scores corresponding to greater perceived importance (Cronbach's alpha 0.58) [33].

2.2.6. Self-efficacy

Self-efficacy was assessed using four study-adapted questions based on those developed by Rosenberg and colleagues [34]. Questions included whether participants felt they would be able to cope with various gene variant outcomes and telling family members about potentially inherited gene variants. Greater scores indicated greater ability to cope with gene variant outcomes (Cronbach's alpha 0.88).

2.2.7. Perceived susceptibility

A validated scale [35], comprising a 5-point Likert scale ranging from '*Much lower*' (0) to '*Much higher*' (4), was used to assess participants' perceived susceptibility of a) having another cancer diagnosis/developing cancer and b) having a gene variant linked to cancer risk, compared to an average person of the same age and gender as them. Participants also rated their perceived susceptibility of having another cancer diagnosis/developing cancer on a visual analogue scale ranging from 0–100%. Scores were normalized and averaged; higher scores indicate greater perceived susceptibility (Cronbach's alpha 0.78).

2.2.8. Attitude toward uncertainty

The seven-item scale from Braithwaite and colleagues was used to assess participants' desire for certainty regarding medical tests [36], where higher scores indicate a greater desire for certainty.

2.2.9. Satisfaction with decision

The scale was used to assess how satisfied participants were with their decision to undergo GS [37]; higher scores indicate higher decisional satisfaction.

2.3. Analyses

Descriptive statistics were used to summarize the data. IBM SPSS Statistics (version 25) was used for data analyses. A multiple linear regression analysis was conducted with GS knowledge score as the outcome variable, and an ordinal regression was conducted with average behavioral intention scores as the outcome variable. Education was treated as an interval variable, so the regression coefficient represents the mean change with each increase in education level (i.e. completed Year 11 or 12 versus vocational training). Knowledge scores were normally distributed in both the probands and relatives (D'Agostino and Pearson normality test).

As summary scores for behavioral intention were negatively skewed, the scores were categorized into four ordered categories; i) <3, ii) ≥3 and <4, iii) ≥4 and <5, and iv) 5. The predictor variables for both regression analyses included the demographics listed above. Perceived importance of GS, satisfaction with decision to have GS,

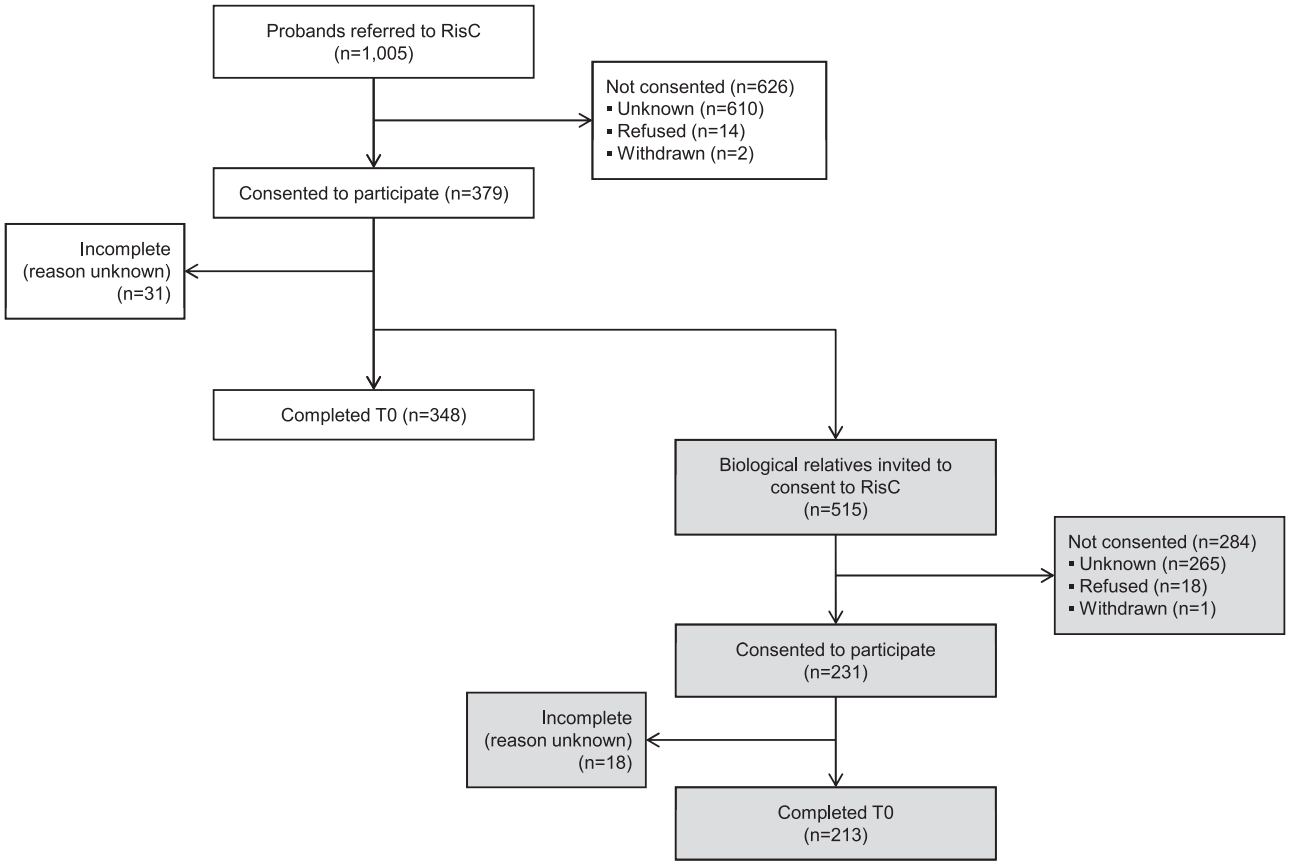

Fig. 1. Flowchart detailing participants' referral, consent and questionnaire completion in the RisC Study.

self-efficacy, perceived susceptibility and attitude to uncertainty measures were included as predictors of GS knowledge, in line with PMT. All variance inflation factors were below 10, indicating no collinearity issues for these predictors. Missing data was handled in the regression using complete case analysis, which resulted in sample sizes for the regressions presented in Tables 2 and 3 of 301 and 190 for probands and relatives, respectively. This corresponds to 86% and 89% of the full cohort respectively.

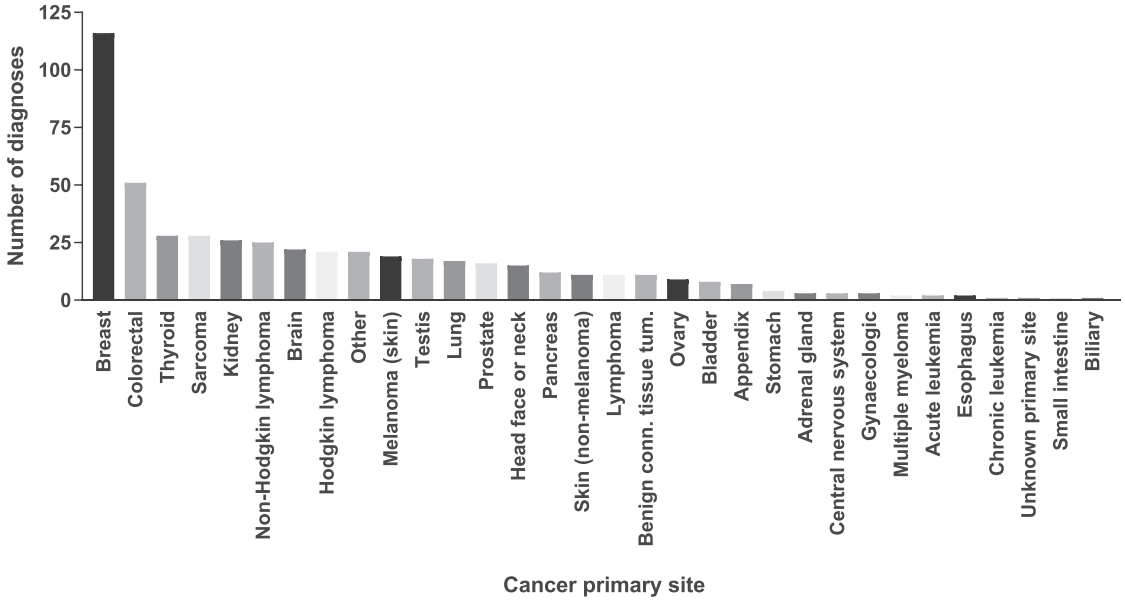

Fig. 2. Primary cancer sites of probands. Number of instances of each cancer type is indicated. Total number of cancers in 348 probands is 515 due to participants having multiple primary cancers. Benign conn. tissue tum.: Benign connective tissue tumors.

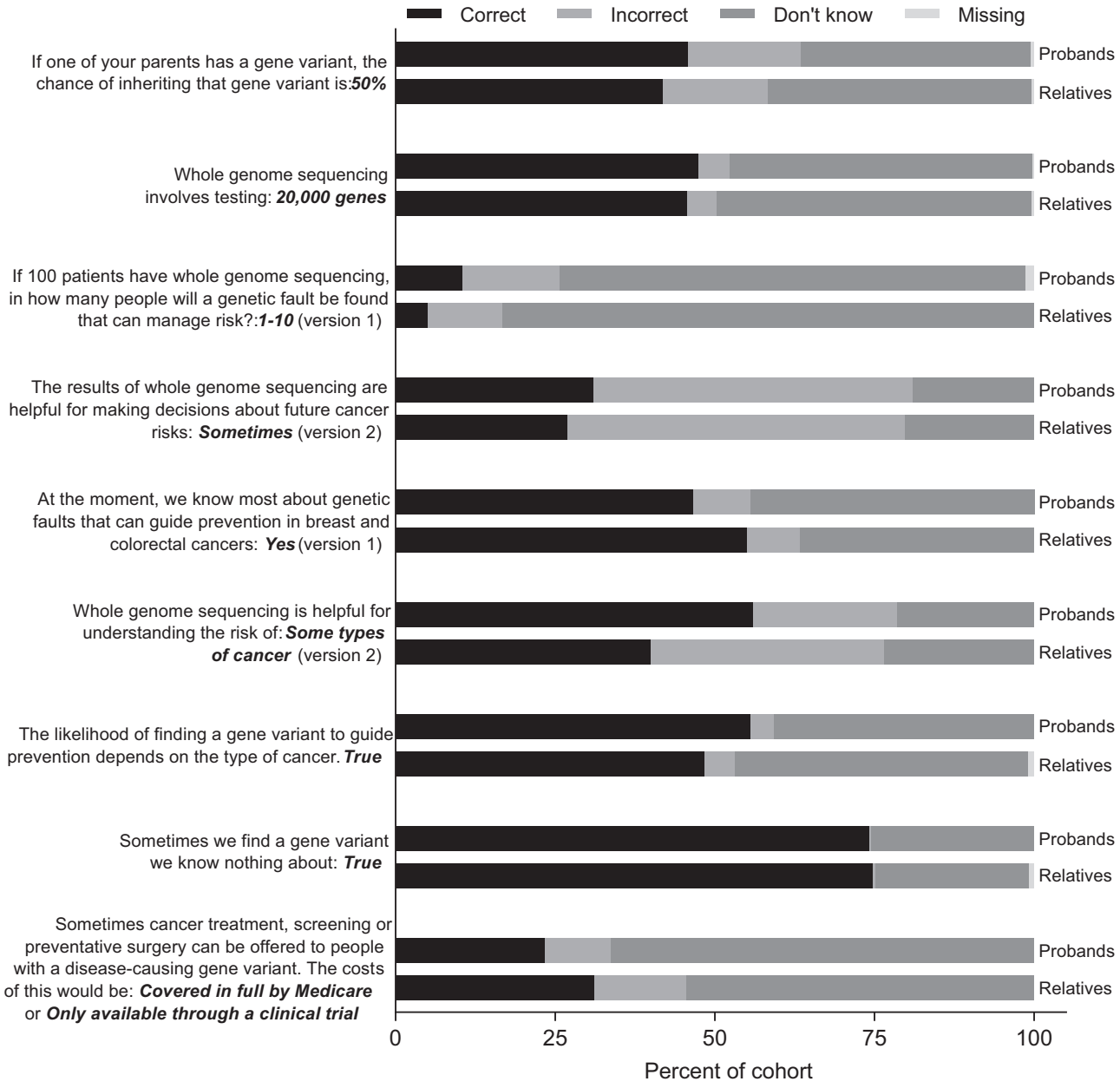

Fig. 3. Study-developed genome sequencing knowledge questions. Correct answers to each item are indicated in bold and italics. Two questions were changed between versions 1 and 2 of the questionnaire. N = 348 for probands and N = 213 for relatives, except version 1 questions (N = 144 for probands and N = 60 for relatives) and version 2 questions (N = 204 for probands and N = 153 for relatives).

3. Results

3.1. Cohort description

Between August 2016 and August 2019, 379 probands and 231 biological relatives were consented to the RisC study. Survey completion rates were 348/379 (92%) and 213/231 (92%) for probands and relatives, respectively (Fig. 1). Relatives consisted mostly of parents (207/213), with the remaining six participants being children or siblings of the proband. Descriptive statistics of both probands and relatives are reported in Table 1. Over 70% of the participants had a rare or less common cancer, defined as cancers with an incidence of < 6 or < 12/100,000 population, respectively. Rare and less common cancer types included those arising from bone and soft tissue (sarcomas), brain, pancreas, kidney, thyroid, appendix and adrenal gland (Fig. 2).

3.2. Knowledge of GS

Probands and relatives had similar knowledge scores at baseline (mean = 45% and 43%, respectively). Three-quarters of both probands and relatives correctly answered the question "*Sometimes we find a gene variant we know nothing about*", and approximately half of probands and relatives correctly identified the number of genes in the genome, likelihood of transmission of a genetic variant, and that clinical utility of genetic risk of cancer depends on the cancer type (Fig. 3). However, 90% of probands and 95% of relatives either did not know or gave an incorrect answer to the question *"If 100 patients have whole genome sequencing, in how many people will a genetic fault be found, that can manage risk"* (answer: 1–10 people), and over two-thirds of probands and relatives did not know that GS was only sometimes helpful for making decisions about future cancer risks. Univariate results suggested a difference in knowledge between

Table 1
Descriptive statistics.

	Probands (N = 348) N, %	Relatives (N = 213) N, %
Demographics		
Sex		
Female	230 (66%)	126 (59%)
Male	118 (34%)	87 (41%)
Age (years)		
Mean (SD)	41.82 (13.72)	63.13 (8.48)
Median (IQR)	39 (17)	64 (11)
Range	16–83	31–87
Education		
Primary school	0	1 (0.5%)
Year 7 or 8	2 (0.6%)	11 (5%)
Year 9 or 10	23 (7%)	43 (20%)
Year 11 or 12	40 (11%)	19 (9%)
Vocational Training	56 (16%)	42 (20%)
University did not graduate	29 (8%)	13 (6%)
University graduated	197 (57%)	82 (38%)
Missing	1 (0.3%)	2 (1%)
Medical/science occupation		
Yes	28 (8%)	16 (8%)
Non-English-speaking background		
Yes	77 (22%)	22 (10%)
Socio-economic status		
Mean (SD)	7.63 (2.56)	6.62 (2.83)
Range	1-10	1-10
Accessibility and Remoteness Index of Australia		
Urban	326 (94%)	180 (85%)
Marital status		
Married	183 (53%)	163 (77%)
Biological children		
Yes	183 (53%)	
Cancer history		
Visited a family cancer clinic		
Yes	91 (26%)	22 (10%)
Family history of cancer		
Yes	287 (83%)	213 (100%)
Cancer diagnosis		
Yes	348 (100%)	49 (23%)
Multiple primary cancers		
Yes	97 (28%)	
Time since first cancer diagnosis (years)		
Mean (SD)	7.45 (9.28)	
Median	3.83	
Range	0–52.17	
Cancer incidence		
Common	100 (29%)	
Less common	25 (7%)	
Rare	223 (64%)	
	Probands (N = 348) N, %	**Relatives (N = 213) N, %**
Behaviors/attitudes		
Knowledge		
Mean (SD)	45% (25%)	43% (25%)
Range	0–100%	0–86%
Behavioral intentions		
Mean (SD)	4.26 (0.69)	4.21 (0.62)
Range	1-5	1-5
Perceived importance		
Mean (SD)	3.77 (0.55)	3.75 (0.54)
Range	1.40–5	2-5
Satisfaction with decision		
Mean (SD)	4.34 (0.54)	4.26 (0.54)
Range	1.33–5	3-5
Attitude toward uncertainty		
Mean (SD)	4.02 (0.70)	3.84 (0.70)
Range	1.57–5	1.43–5
Self-efficacy		
Mean (SD)	4.13 (0.69)	4.14 (0.64)
Range	1-5	2-5
Perceived susceptibility		
Mean (SD)	64.03 (18.09)	47.09 (16.49)
Range	0–100	0–100

SD: standard deviation; IQR: interquartile range

probands with secondary only vs vocational training or university education ($p = 0.05$), and a highly significant difference in relatives ($p < 0.001$) (Fig. 4).

A multiple linear regression revealed that higher levels of education, previous attendance at an FCC, and being married were significant predictors of probands' GS knowledge scores (Table 2). Predictors of GS knowledge scores for relatives included: a greater level of education, a medical or science occupation, and greater self-efficacy. Every categorical increase in education level (i.e. completed Year 11 or 12 compared to post-secondary education) led to knowledge score increases of 2.5% for probands (95% CI: 0.40–4.59, $p = 0.020$) and 2.8% for relatives (95% CI: 0.56–4.98, $p = 0.015$). Furthermore, probands who had previously visited an FCC or were married, were predicted to have an 8% higher GS knowledge score (FCC - 95% CI: 2.01–14.19, $p = 0.009$; married - 95% CI: 1.82–14.08, $p = 0.011$).

Similarly, there was an 8% increase in relative's GS knowledge score for each categorical increase (i.e. '*Agree*' to '*Strongly agree*') in relatives' perceived self-efficacy to cope with results (95% CI: 2.27–14.39, $p = 0.007$). Relatives with a medical or science occupation scored 16% higher with regard to their knowledge of GS compared to relatives without a medical or science occupation (95% CI: 3.43–29.10, $p = 0.013$), which was the greatest increase in GS knowledge score predicted by any variable within either of the two cohorts.

3.3. Intention to change behavior

Overall, both probands and relatives indicated having strong intentions to change their behaviors (means = 4.26 and 4.21, respectively, out of a possible score of 5; Table 1). More than half of both probands and relatives '*Strongly agreed*' that they intended to seek more information if a gene variant linked to cancer risk was identified via GS. In contrast, only 35% and 28% of probands and relatives, respectively, reported strong intentions ('*Strongly agree*') to change the amount of alcohol consumed in response to learning they carried a cancer-risk associated gene variant (Fig. 5).

Ordinal regression analyses revealed that gender and higher perceived importance of GS were significant predictors of intention to change behavior for both probands and relatives. Specifically, the ordered odds of females having greater intention to change behavior was 1.93 times (95% CI: 1.16–3.19, $p = 0.011$) for probands, and 2.29 times (95% CI: 1.19–4.38, $p = 0.013$) for relatives, compared to males (Table 3). For each categorical increase in perceived importance of GS (i.e. '*Agree*' to '*Strongly agree*'), the ordered odds of having greater intention to change behavior increased by 3.80-fold (95% CI: 2.43–5.94, $p < 0.001$) for probands and by 3.71-fold (95% CI: 2.00–6.89, $p < 0.001$) for relatives. Knowledge levels did not predict intent to change behavior for either probands (95% CI: 0.26–1.92, $p = 0.490$) or relatives (95% CI: 0.16–2.07, $p = 0.391$).

For probands, additional predictors of greater intention to change behavior included: being from an English-speaking background, higher SES, higher self-efficacy and having higher negative attitudes towards uncertainty. The ordered odds of probands from an English-speaking background having greater intentions to change behavior was 2.51 (95% CI: 0.98–1.12, $p = 0.003$) times that of participants from a non-English-speaking background. For every one-unit

Table 2
Summary of regression analyses for variables predicting knowledge about GS.

Independent variables	Probands		Relatives	
	Regression coefficient (95% CI)	*p* value	Regression coefficient (95% CI)	*p* value
Sex				
Female (Ref. category: Male)	4.66 (−1.25 to 0.11)	0.121	-0.09 (−7.60 to 7.41)	0.980
Age (for every 10 year increase)	0.97 (−2.19 to 4.12)	0.547	-1.26 (−5.85 to 3.34)	0.590
Education	2.49 (0.40–4.59)	0.020*	2.77 (0.56–4.98)	0.015*
Medical/science occupation				
Yes (Ref. category: No)	6.88 (−2.55 to 16.32)	0.152	16.26 (3.43–29.10)	0.013*
English-speaking background				
Yes (Ref. category: No)	4.42 (−2.45 to 11.30)	0.207	-0.95 (−12.96 to 11.06)	0.876
Socio-economic status	-0.03 (−1.17 to 1.10)	0.952	-0.02 (−1.37 to 1.38)	0.982
Accessibility and Remoteness Index of Australia				
Urban (Ref. category: Remote)	6.79 (−6.44 to 20.01)	0.313	3.04 (−9.98 to 16.06)	0.645
Previous visit to a family cancer clinic				
Yes (Ref. category: No)	8.10 (2.01–14.19)	0.009**	6.81 (−4.58 to 18.21)	0.240
Married				
Yes (Ref. category: No)	7.95 (1.82–14.08)	0.011*	-5.48 (−13.85 to 2.88)	0.197
Biological children				
Yes (Ref. category: No)	-2.88 (−9.99 to 4.23)	0.427		
Family history of cancer				
Yes (Ref. category: No)	6.91 (−1.05 to 14.86)	0.089		
Cancer diagnosis				
No (Ref. category: Yes)			2.50 (−6.01 to 11.00)	0.563
Multiple primary cancers				
Yes (Ref. category: No)	4.77 (−3.49 to 13.03)	0.257		
Time since diagnosis	-0.30 (−0.66 to 0.07)	0.116		
Cancer incidence				
Common	-0.77 (−6.98 to 5.44)	0.808		
Less common	4.58 (−5.48 to 14.64)	0.371		
Rare	Ref. category			
Behavioral intentions	-3.72 (−8.22 to 0.78)	0.104	-2.28 (−8.77 to 4.22)	0.490
Perceived importance	2.90 (−2.36 to 8.16)	0.279	-0.62 (−7.86 to 6.62)	0.866
Satisfaction with decision	1.63 (−5.13 to 8.40)	0.635	0.51 (−8.10 to 9.09)	0.906
Self-efficacy	2.08 (−2.36 to 6.52)	0.357	8.33 (2.27–14.39)	0.007**
Perceived susceptibility (10 units scaled)	-1.24 (−2.76 to 0.27)	0.107	0.46 (−1.74 to 2.66)	0.682
Attitude toward uncertainty	-3.36 (−7.88 to 1.17)	0.145	-4.61 (−10.61 to 1.40)	0.132

Ref. = reference
* $p < 0.05$;
** $p < 0.01$.

increase in the remaining variables there was an increase in intention by a factor of 1.14 (95% CI: 1.03–1.25, p = 0.010) for SES; 1.58 (95% CI: 1.08–2.28, p = 0.017) for self-efficacy; and 1.73 (95% CI: 1.17–2.55, p = 0.006) for negative attitudes toward uncertainty.

The analysis among the relatives cohort revealed that not having a personal cancer diagnosis and reporting greater satisfaction with the decision to have germline GS, were associated with greater intentions to change behavior. Relatives lacking a personal cancer diagnosis were more likely (2.39 times; 95% CI: 1.16–4.95) to have greater intentions to change their behavior compared to those who had faced their own cancer diagnosis. For each category increase in relatives' satisfaction with their decision to have germline GS, the ordered odds of having greater intention to change behavior increased by 3.33-fold (95% CI: 1.60–6.92, p = 0.001).

Posthoc univariate analyses explored whether particular knowledge items were more strongly associated with behavioral intentions. Knowing that GS is helpful for making decisions about future cancer risks ($p < 0.05$, Dunn's multiple comparisons test) and that the likelihood of finding a gene variant to guide prevention depends on the type of cancer ($p < 0.05$, Dunn's multiple comparisons test) were associated with greater intentions to change behavior.

4. Discussion and conclusion

4.1. Discussion

Our study reports on a cancer-affected (personal or familial) population who consented to germline GS as part of a larger research study investigating heritable cancer risk, identified by virtue of earlier age at cancer onset, or the presence of multiple primary cancers, rather than family history. Specifically, we assessed participants' knowledge of germline GS and intention to change behavior if they were to receive a pathogenic variant finding linked to cancer risk.

4.2. Knowledge

Overall, participants' knowledge of germline GS was moderate, with participants scoring on average less than 50% on the study-designed knowledge scale. Many participants over-estimated the likelihood of obtaining an actionable result, and the utility of GS in cancer. Unrealistic expectations of GS, which can result in disappointment, anxiety and decisional regret when these are not realized [7], are common among patients undergoing GS in both research and diagnostic settings [38–41]. In one study, many participants believed results would give them an absolute answer on whether or not they would develop a specific disease. Unrealistic expectations arise from the complexity and uncertainty inherent in genomic results [42]. Several authors have suggested strategies at both consent and return of results, to ensure patient expectations are more accurate. These include repeating information, providing written, personalized information and checking understanding [42].

Higher GS knowledge was predicted by higher levels of education in both groups. These results are in accord with previous studies correlating education and GS knowledge, albeit in different patient populations and using different knowledge scales [8,11,13,32]. We found probands' previous attendance at an FCC was also predictive of GS knowledge, consistent with findings of Rini and colleagues [8].

Table 3
Summary of regression analyses for variables predicting behavioral intentions.

Independent variables	Probands		Relatives	
	Regression coefficient (95% CI)	*p* value	Regression coefficient (95% CI)	*p* value
Sex				
Female (Ref. category: Male)	1.93 (1.16–3.19)	0.011*	2.29 (1.19–4.38)	0.013*
Age (for every 10 year increase)	0.89 (0.68–1.17)	0.429	1.25 (0.98–1.86)	0.266
Education	0.88 (0.74–2.30)	0.181	1.04 (0.86–1.26)	0.683
Medical/science occupation				
Yes (Ref. category: No)	0.53 (0.24–1.18)	0.119	1.17 (0.38–3.62)	0.789
English-speaking background				
Yes (Ref. category: No)	2.51 (0.98–1.12)	0.003**	0.81 (0.29–2.28)	0.691
Socio-economic status	1.14 (1.03–1.25)	0.010**	1.04 (0.92–1.17)	0.524
Accessibility and Remoteness Index of Australia				
Urban (Ref. category: Remote)	0.42 (0.13–1.30)	0.133	0.80 (0.26–2.42)	0.688
Family cancer clinic				
Yes (Ref. category: No)	0.90 (0.53–1.53)	0.705	0.76 (0.29–2.02)	0.581
Married				
Yes (Ref. category: No)	1.17 (0.69–2.20)	0.559	1.27 (0.62–2.60)	0.517
Biological children				
Yes (Ref. category: No)	1.15 (0.63–2.13)	0.649		
Family history of cancer				
Yes (Ref. category: No)	1.58 (0.80–3.14)	0.188		
Cancer diagnosis				
No (Ref. category: Yes)			2.39 (1.16–4.95)	0.018*
Multiple primary cancers				
Yes (Ref. category: No)	1.64 (0.80–3.35)	0.173		
Time since diagnosis	0.97 (0.94–1.00)	0.052		
Cancer incidence				
Common	1.19 (0.70–2.02)	0.530		
Less common	1.06 (0.44–2.51)	0.903		
Rare	Ref.			
Perceived importance	3.80 (2.43–5.94)	<0.001***	3.71 (2.00–6.89)	<0.001***
Satisfaction with decision	1.28 (0.72–2.30)	0.398	3.33 (1.60–6.92)	0.001***
Self-efficacy	1.58 (1.08–2.29)	0.017*	0.91 (0.53–1.54)	0.723
Perceived susceptibility (10 units scaled)	0.92 (0.81–1.05)	0.239	0.92 (0.76–1.11)	0.382
Attitude toward uncertainty	1.73 (1.17–2.55)	0.006**	1.58 (0.94–2.65)	0.085
Knowledge	0.70 (0.26–1.92)	0.490	0.57 (0.16–2.07)	0.391

Ref. = reference
* $p < 0.05$;
** $p \leq 0.01$;
*** $p \leq 0.001$.

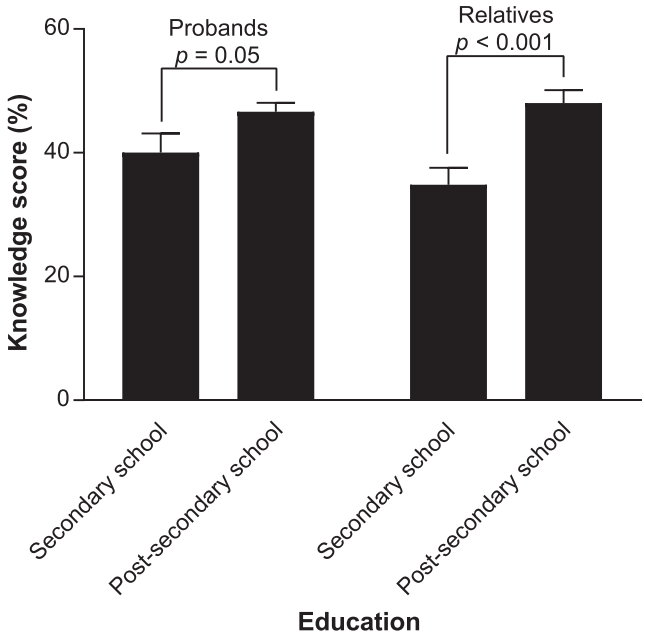

Fig. 4. Baseline knowledge score and highest level of education. Knowledge scores of those having completed secondary school (years 7–12) versus attended post-secondary school (vocational training or university). Data indicate mean ± standard error of the mean. P values calculated using an unpaired *t*-test.

This association may reflect the efficacy of education within FCCs, or that those with higher knowledge are more likely to attend an FCC. However, the feasibility of all research study participants attending FCCs to become more educated about GS and its potential results/implications is low due to limited resources at these centers. This suggests that research and oncology staff will need upskilling to provide more effective education, if participant knowledge is to improve. Previous attendance at an FCC was not predictive of GS knowledge for relatives. Perhaps relatives feel their family role is to support the adult proband as opposed to learning about GS during FCC visits.

Our expectation that higher GS knowledge would be associated with demographics including higher SES, living in an urban area and speaking English at home was not supported. This could be due to the majority of the cohort living in an urban area with a high SES, and perhaps, language is not a barrier to learning about GS. Furthermore, having a family history of cancer, a more recent cancer diagnosis or a rare cancer type was also not associated with GS knowledge. These potential correlates were included as it was thought they would precipitate discussions about cancer within the family and encourage information-seeking about the potential utility of GS (for heritable or treatment information). Additionally, associations between perceived cancer susceptibility and importance of GS, attitude toward uncertainty and satisfaction with decision and GS knowledge were not supported, perhaps due to a lack of variation in these variables, with most participants reporting high susceptibility, high perceived importance of GS, negative attitude toward uncertainty and high satisfaction with the decision to have GS.

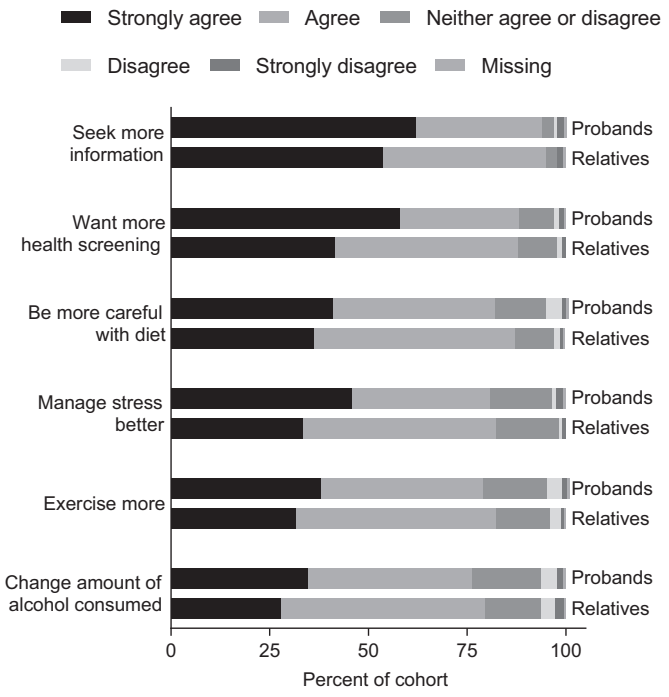

Fig. 5. Intention to change behavior responses. Participants were asked whether they would change the indicated behavior if they knew they had inherited gene variants that increased cancer risk. N = 348 for probands and N = 213 for relatives, except "Change amount of alcohol consumed", which excludes participants that do not regularly drink alcohol (N = 214 for probands and N = 141 for relatives).

It is also possible that our study-developed knowledge scale was insufficiently sensitive to identify key issues of importance to cancer patients undertaking GS. In the time since the current study design in 2016, additional validated knowledge measures have been developed including the University of North Carolina Genomic Knowledge Scale (UNC-GKS) [43] and Knowledge of Genome Sequencing (KOGS) scale [44]. These scales examine knowledge in the domains of genes, sequencing and heritability. Future studies using either the UNC-GKS or KOGS scales will provide additional information as to knowledge gaps which education needs to target.

4.3. Change in behavior

The current study adds to an existing literature base regarding intention to change behaviors based on germline GS results [45–47], and is unique in that all participants had a personal or familial experience of cancer, with the majority being rare and less common cancers. The strong overall intention to change behavior we observed aligns with the expectation that participants with personal experience of cancer (self or family) would be highly motivated to perform risk-reducing behaviors [48]. Our finding that females were twice as likely as males to intend to change behaviors based on GS results is in keeping with previous studies where females were more likely to engage in health-promoting behaviors, including sunscreen use, eating a healthy diet and reducing alcohol consumption [49–51].

Being from an English-speaking household and higher SES were also associated with greater behavioral change intentions for probands. Previous reports indicate that being from a non-English-speaking household is associated with decreased screening for cancers such as breast and bowel cancers [52], and there is lower uptake of cervical cancer screening in areas of lower SES [53]. It has been suggested that individuals from low SES feel less in control of their environment [54], and therefore less autonomy to change behavior. Another study found that immigrants are often living with complex transnational ties and obligations that leave little room for personal health as a priority [55]. Learning the reasons why these subgroups are less likely to intend behavioral change is vital to realizing equitable benefits of GS. Furthermore, increasing knowledge may help these vulnerable groups, but our results suggest this is not sufficient, and other interventions to overcome disadvantage may be needed.

Proposed predictors of intention to change behavior that were not supported by the current study include education level, a medical or science occupation and living in an urban environment. These results are encouraging, as they suggest that where one lives and one's level of education do not need to be barriers to improving lifestyle behaviors such as diet, exercise, alcohol consumption and stress reduction. Furthermore, previously attending an FCC, having a family history of cancer, more recent diagnosis of cancer, and a rare cancer type were not associated with intention to change behavior. These results indicate that personal, lived experience with any cancer diagnosis may impact intention to change behavior more than the more specific cancer-associated factors assessed.

In line with the PMT proposition that perceived efficacy of a preventive behavior and higher self-efficacy to undertake that behavior will lead to greater intention to change, perceived importance of GS and higher self-efficacy were found to be predictive of probands', but not relatives', intention to change behavior. Probands, unlike relatives (most of whom did not have cancer), may have already tried to make behavior changes to impact their cancer outcomes, so thus have learned about their own self-efficacy in making these changes. Furthermore, analyzing probands' intention to change behavior based on cancer types that are and are not potentially modifiable by lifestyle (e.g. colorectal vs pancreas) revealed no differences.

The third element of PMT theory (perceived threat, assessed here by perceived susceptibility to cancer) was surprisingly not found to be associated with behavioral intention, perhaps due to the lack of variability in participants' responses (> 70% of participants scored ≥ 50 on perceived susceptibility) and thus warrants exploration in future research. In their meta-analysis of studies testing PMT in predicting health-related behavior, Milne and colleagues [56] found the relationship between perceived susceptibility and behavioral intention was small, with efficacy variables having a larger effect. They posited that while feeling vulnerable may motivate behavior, enacting the behavior may lessen/remove this sense of vulnerability, thereby removing the effect.

Relatives' (but not probands') satisfaction with their decision to have GS was highly predictive of intention to change behavior. Relatives' satisfaction may relate to being highly motivated to make behavior changes on the basis of genetic results. Conversely, probands may have already made behavior changes after their cancer diagnosis; their satisfaction with the decision to have GS may relate more to understanding the etiology of their cancer diagnosis than to future risk and behavior to avert it.

Limitations of the current study include the cross-sectional analysis, which means that associations cannot be assumed to be causative. Some measures utilized were study-developed (in the absence of existing, validated measures) or adapted from other scales to address the specific study scenario, and may not have fully or reliably assessed study variables. Reliability and validity of the knowledge scale were not assessed, and the scale asked study participants to indicate the likelihood of some outcomes, which required familiarity with percentages as a measure of likelihood. In addition, the perceived importance of GS measure had a Cronbach's alpha of 0.58, indicating that it may lack internal consistency. It is not entirely clear whether knowledge assessed was background knowledge or obtained during the consent process. One of the seven items in the knowledge questionnaire was covered in the information sheet (that whole genome sequencing

involves testing 20,000 genes). However, we cannot be certain that other issues did not come up during informal discussion during the consent process.

Finally, future longitudinal analyses that incorporate actual behavior change are needed to further explore and corroborate our findings regarding hypothetical intentions. The well-established intention-behavioral gap demonstrates that despite firm intentions to change behavior, this is often not realized [57]. However, as researchers and health professionals often wish to identify and refine behavior change strategies early, when behavioral outcome data is not yet available, intention to change is still a worthy outcome to explore. Furthermore, a meta-analysis of 47 studies found that while the intention-behavior gap is a real phenomenon, a medium-to-large change in intention leads to a small-to-medium change in behavior, providing some predictive power [58]. Various strategies have been suggested to bridge this gap, including increasing self-efficacy, detailed planning, and controlling one's behavior [59], which may be explored in future studies.

4.4. Conclusion

Our study is the first to examine both knowledge and behavioral intentions in an Australian population affected by mostly rare and less common cancers (either self or family) undergoing germline GS to determine gene variants associated with cancer risk. Future studies examining whether receiving a germline GS result that indicates a gene variant linked to cancer risk actually changes an individual's behavior, are warranted. The current findings are the first step towards determining whether germline GS in a cancer risk population is worth the expense to the individual and/or the healthcare system, via behavioral change.

4.5. Practice implications

Our finding that participants had only moderate GS knowledge identifies a need for increased education regarding the benefits and limitations of GS in order to align patient expectations with likely outcomes. Such educational resources may include plain language summaries taken home from consent appointments or web-based learning [60] and need to be targeted and accessible to all groups, including those from non-English speaking and low socio-economic backgrounds. Furthermore, patient-specific support such as smartphone apps and access to support personnel [61,62] to encourage, facilitate and maintain behavior change intentions should be employed in individuals identified with a gene variant linked to increase cancer risk.

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CRediT authorship contribution statement

Christine Napier: Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Grace Davies:** Formal analysis, Writing – review & editing. **Phyllis Butow:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Timothy Schlub:** Formal analysis, Methodology. **Megan Best:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing. **Nicci Bartley:** Project administration, Writing – review & editing. **Ilona Juraskova:** Conceptualization, Methodology, Writing – review & editing. **Bettina Meiser:** Conceptualization, Methodology, Writing – review & editing. **Katherine M. Tucker:** Writing – review & editing. **Barbara Biesecker:** Conceptualization, Writing – review & editing. **David Thomas:** Conceptualization, Funding acquisition, Resources, Writing – original draft, Writing – review & editing. **Mandy Ballinger:** Conceptualization, Funding acquisition, Resources, Supervision, Writing – original draft, Writing – review & editing.

Other declarations

I confirm all personal identifiers have been removed or disguised so the persons described are not identifiable and cannot be identified through the details of the story.

Declaration of Competing Interest

The authors have no conflicts of interest to declare. BM and KT have remunerated consultant roles with the company AstraZeneca with respect to unrelated projects.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.pec.2021.07.004.

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