**Study Protocol:**

**Psychosocial Aspects of Genomic Testing for Breast Cancer Risk**

Version Number: 5

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SYNOPSIS

**Protocol title:** Psychological and behavioural impact of genomic testing for breast cancer risk

**Protocol version:** 4

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SPONSOR OF THE PROJECT

University of New South Wales

Cancer Council New South Wales

**Summary**

**Study title:** Psychological and behavioural impact of genomic testing for breast cancer risk

**Protocol version:** Version 5.

**Objectives:** 1. Invite 400 female ViP participants to receive their genomic testing results to determine their interest in accepting this invitation, i.e. uptake of this offer and factors associated with uptake; and

 2. Assess the short- and long-term psychological and behavioural outcomes, including compliance with recommended screening and preventative strategies, of women who receive their results (‘receivers’) and those who decline to do so (‘decliners’).

 3. Invite up to 40 receivers to participate in-depth, semi-structured telephone interviews and explore their experience receiving their genomic testing results.

**Study design:** Mixed methods, including questionnaires and in depth interviews.

**Planned sample size:** 400

**Selection criteria:** Women who are participating in the parent study ‘Common Genetic Variants and Familial Cancer’ study (commonly known as Variance in Practice, ViP) will be invited to take part in this psychosocial study.

Inclusion criteria: index participants with a personal diagnosis of breast cancer and family members with and without a personal history of breast cancer. Women with a low or high polygenic risk score (PRS) will be included.

 Exclusion criteria include: women where a rare high-risk gene mutation has been identified (e.g *BRCA1* or *BRCA2*) in their families and men. Women must be able to read and/or converse proficiently in English and provide informed consent.

**Study procedure:** Women selected for inclusion in the study will be invited by letter to receive their PRS result and will simultaneously be invited into the Psychosocial Study. Women who do not opt out will be sent questionnaire 1. Twelve months after receipt of the initial notification letter, participants who did not receive their PRS result will be asked to complete questionnaire 3. Participants who attend an FCC to receive their PRS result will be asked to complete questionnaires 2 and 3, two weeks and 12 months after their appointment respectively.

 Forty participants who opted to receive their test results will also be invited to participate in semi-structured telephone interviews. Interviews will be scheduled around 2 weeks after participants received their test results. Participants will have an option to opt-out of this additional study.

 All genetic counselling consultations associated with this research study at the Peter MacCallum Cancer Centre and Royal Melbourne Hospital will be recorded. The recorded consultations will be transcribed and subjected to communication and behavioural analysis.

**Analysis plan****:** Data will be analysed using SPSS 22.0 (Statistical Program for Social Sciences). Basic descriptive statistics will be used to describe the sample. The means of baseline key variables will be compared between subgroups. For each of the main outcome variables regression analysis will be used as appropriate. Further multivariate analyses will be used to adjust for potential confounding variables and to investigate outcomes between subgroups.

 Qualitative data will be analysed for themes using NVivo, a qualitative data analysis program.

**Duration of the study:** January 2016 – December 2018

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**List of Abbreviations**

BRCA1/2 Breast cancer gene 1 and 2

FCC Familial Cancer Clinic

GWAS Genome wide association studies

PRS Polygenic Risk Score

ViP Variance in Practice Study (formal title: “Common genetic Variants and Familial Cancer Cohort”)

SNPs Single Nucleotide Polymorphism

# Background

## Breast Cancer

Breast cancer is the greatest cause of premature death due to chronic disease in Australian women, accounting for approximately 12% of all premature deaths [[1](#_ENREF_1)]. Any intervention that reduces the morbidity and mortality of breast cancer has the potential to make a significant impact on disease burden. Between 10% and 20% of breast cancer is associated with a family history of breast and/or related cancers (termed hereditary breast cancer) [[2](#_ENREF_2)]. Hereditary breast cancer is clinically important due to the availability of effective risk management strategies that can be targeted to certain subgroups of high-risk women (e.g. breast magnetic resonance imaging and risk-reducing surgery) [[3](#_ENREF_3), [4](#_ENREF_4)]. Since familial cancer clinics (FCC) were first established in the early 1990’s in Australia, practice has focussed on the molecular diagnosis of high-penetrance (*BRCA1/2, TP53, PTEN*) and moderate-penetrance (*PALB2, RAD51C, BRIP1*) gene mutations which were discovered through family linkage or candidate approaches. However, such testing is only informative in about 15-20% families tested, which means that current testing does not provide clinically useful information for the majority of families where the risk of hereditary breast cancer is potentially high [[5](#_ENREF_5)]. In these cases the final risk assessment and screening advice is not personalised but based on empiric family history data and extrapolated from population epidemiological studies [[6](#_ENREF_6)].

## Common risk variants in breast cancer

The ‘common variant, common disease’ model predicts that a significant component of hereditary breast cancer that cannot be explained by high or moderate-penetrance gene mutations is due to the cumulative effect of multiple common risk variants in DNA (single nucleotide polymorphisms, SNPs) [[5](#_ENREF_5)]. On their own, each of these common risk variants only slightly increases breast cancer risk; however if these small effects from a number of variants combine, breast cancer risk can be significantly increased (‘polygenic risk’) [[7](#_ENREF_7)]. More than 80 risk-associated SNPs have been found in large high-quality breast cancer genome wide association studies (GWAS) (e.g. [[8](#_ENREF_8)]).

A recent Australian study, the “Common genetic Variants and Familial Cancer Cohort” utilised the Victorian Familial Breast Cancer Cohort to identify 1,143 women who had previously had breast cancer and undergone *BRCA* testing and were not identified as carrying any know BRCA mutations. Genotyping of 22 breast cancer associated genomic variants or SNPs was undertaken and a polygenic risk score (PRS) was constructed and compared to a normal distribution in appropriate control groups [23]. A subset of women were identified with a genetically defined high familial risk who have particular clinical characteristics including: increased frequency of early onset cancers, approximately two-fold increase in the rate of a contralateral breast cancer diagnosis, less than half the risk of a *BRCA1/2* mutation and no increased risk of ovarian cancer [23].

Testing for common risk variants has the potential to provide information about the cumulative polygenic risk component of breast cancer and addresses other important clinical questions in this group. For example, women assessed as high risk by their PRS can be advised about the availability of effective risk management strategies, including regular breast cancer screening (at a younger age than recommended for others), risk-reducing medication if not otherwise indicated by their primary breast cancer pathology and risk-reducing mastectomy. By contrast, women assessed as low risk can be reassured that breast conservation and usual-care screening levels are appropriate. Similarly, women who receive an intermediate risk can be advised that their PRS results does not change their breast cancer risk status and hence risk management advice.

## Common Genetic Variants and Familial Cancer Cohort

Women enrolled in the “Common genetic Variants and Familial Cancer” study (commonly known as ‘Variants in Practice’ (ViP)) provide a unique cohort in which to systematically ascertain the important psychosocial and clinical implications of genomic testing and to answer a large number of research questions at a small cost. The ViP study (HREC/11/PMCC/43) is enrolling a cohort of over 4,000 Victorian women and men who have a high-risk family history of breast cancer, this includes index cases with a personal history of breast cancer and their affected and unaffected relatives (Appendix P). To date approximately 3700 of the total study cohort had genomic testing for approximately 90 common risk variants already known to be associated with breast cancer risk. The study aims to complete genomic testing for all study participants.

Prior to enrolment in ViP study, all index cases will have attended one of the participating FCCs and undergone clinical assessment which includes testing for *BRCA1/2* gene mutation. Index cases may also have had genetic testing for other genes (e.g *TP53* and *PTEN*) depending on their family history and phenotype. Index cases are recruited retrospectively and prospectively.

For retrospective enrolment, patients who had undergone BRCA mutation detection testing prior to study commencement (<2012) were identified from the databases of participating FCCs. Patients were invited to join the study using an invitation letter that allowed them to indicate whether they wished to be contacted further. Once a signed PICF was received, the research team collected individual demographic data, medical history and family cancer history data from the clinic files and retrieved an aliquot of the diagnostic DNA sample. A small proportion of participants were contacted, after they had consented, to ask for further cancer history information or to ask them to have a blood sample collected because the diagnostic DNA was unavailable. In this retrospective group, approximately 70% of patients who were sent an invitation letter consented to participate in the study. Approximately 15% declined and the remaining patients either could not be contacted or responded interested to the invite but then never returned the PICF.

For prospective enrolment, patients are invited to participate in the study by a genetic health professional during their consult with the clinic (ie. at the time of *BRCA* mutation testing). As with retrospective enrolment, diagnostic DNA and clinic data is collected by the research team once the participant has signed the PICF. There are currently 2700+ indexes participating in the ViP study and recruitment is ongoing.

Most family members were approached by the index themselves. Participating indexes were asked to provide their interested family members with a study invite letter. Family members who returned an invite letter response sheet (with their contact details) were phoned by the research team and subsequently mailed a study PICF and pathology request slip to have a blood (DNA) sample collected at their local pathology collection centre. Family members were asked to provide basic demographic and cancer related data. Unlike the index cases, only a proportion of family members have a personal history of cancer and many have not personally had direct contact with a familial cancer clinic. The ViP study currently has 1540+ family members enrolled.

## Psychological impact of genetic testing for hereditary breast cancer

A review of the literature shows that the majority of studies on the impact of genetic testing for cancer susceptibility assessed women in whose families a specific *BRCA1/2* mutation had already been identified, this represents a minority of at-risk families. These studies show that the uptake of genetic testing for *BRCA1/2* mutations is more consistently related to psychological factors (i.e. cancer anxiety, perceived risk) than to sociodemographic variables [[9](#_ENREF_9)]. Studies on the psychological impact of genetic testing for *BRCA1/2* mutations amongst women with a personal cancer diagnosis (‘affected’ women) demonstrate that non-carriers derive significant psychological benefits from genetic testing, while distress among carriers increases shortly after receiving results but returns to pre-testing levels over time [[9](#_ENREF_9), [10](#_ENREF_10)]. Most data available on the psychosocial impact of testing for high-penetrance mutations in women without a personal diagnosis (‘unaffected’ women) show few adverse psychological effects [[11](#_ENREF_11), [12](#_ENREF_12)]. Regarding its impact on health behaviours, one review article concluded that genetic testing for breast cancer susceptibility is associated with increased adherence to recommended screening and uptake of risk-reducing surgery in subgroups (i.e. carriers, especially affected women) [[13](#_ENREF_13)]. However, other authors have noted considerable variability in uptake of screening and risk-reducing surgery [[9](#_ENREF_9), [14](#_ENREF_14)].

The impact on those for whom testing for high-penetrance gene mutations leads to uninformative results is largely unexplored [[9](#_ENREF_9)]. A minority of affected women misinterpret their result as meaning that the cancers in their family were definitely not caused by a gene mutation [[15](#_ENREF_15)]. These findings suggest that many of the >80% of women who undergo testing for high-penetrance gene mutation and receive uninformative results may feel falsely reassured and misinterpret their results as ‘No news is good news’. For the large group of women who would otherwise receive uninformative results from testing for high-penetrance mutations, the advent of additional testing for common risk variants means that all women can be given risk information based on testing results, thus potentially reducing the risk of false reassurance and of psychological adversity resulting from continuing uncertainty about their risk status.

## Theoretical framework guiding research

Protection Motivation Theory is the theoretical framework guiding this research to identify the predictors of a range of health behaviours, including uptake of genomic testing [[16](#_ENREF_16), [17](#_ENREF_17)]. The theory was developed to address the cognitive processes of individuals that mediate the effect of persuasive communications on behavioural change, through the identification of two independent appraisal processes: threat and coping appraisals. The theory proposes that threat appraisals are based on the individual’s perception of their vulnerability towards, and severity of the undesirable health outcome. Their coping appraisal is centred instead on the perceived costs of their adaptive response: response efficacy and their own self-efficacy towards partaking in the behaviour (Figure 1).

**Figure 1: Protection Motivation Framework**

**Behaviour**

- Concordance with screening guidelines

- Intention to take preventative strategies

**Self-efficacy**

**Response efficacy**

**Vulnerability**

**Threat appraisal**

**Coping appraisal**

**Response cost**

**Severity**

**Fear**

**Protection Motivation**

Intention to receive results

**Demographic, knowledge, uncertainty**

## Clinical challenge

Testing for common risk variants is fundamentally different in nature to testing for the type of genetic information that has been available up to now, and there is little experience in the effective communication of these complex results. The interpretation of individual results depends on: whether or not the woman had a personal diagnosis of breast or a related cancer; the strength of family history; and whether the proband or other family members have been tested for rare high-penetrance mutations [[9-12](#_ENREF_9)]. Research is critical to ensure that results are effectively communicated. This study aims to develop a best-practice model of providing common risk variant results in the hereditary cancer setting, to meet the likely future demand for, and prepare for widespread implementation of genomic testing in cancer.

# STUDY OBJECTIVES

## Rationale for performing the study

This is the world’s first study to assess the impact of offering risk information related to common risk variants to women. If the study demonstrates that results from variant testing can be delivered to this patient group without causing undue psychological adverse outcomes, this will provide support for the safety of widespread clinical implementation of such testing. Additionally, testing for common risk variants will result in a paradigm shift in the practice of clinical genetics and oncology. Currently, referrals to FCCs are on the basis of personal and family history, cancer type and/or other clinical criteria based on the likelihood of a high-penetrance gene mutation being present. However, it is increasingly clear that risk ascertainment based on other types of genetic risk, often in the absence of family history, will dramatically change service provision more widely.

## Aim and hypothesis

**Aim 1.** Invite 400 female ViP participants to receive their genomic testing results to determine their interest in accepting this invitation, i.e. uptake of this offer and factors associated with uptake; and

Hypothesis 1a) Compared to decliners, receivers will:

* 1. have higher baseline breast cancer anxiety (primary outcome variable), a need to avoid uncertainty, and they will be more likely to have daughters;
	2. be more likely to comply with breast cancer screening guidelines 12 months after receiving their results.

**Aim 2.** Assess the short (2 weeks) and long term (12 months) psychological and behavioural outcomes, including compliance with recommended screening and preventative strategies, of women who receive their results (‘receivers’) and those who decline to do so (‘decliners’).

Hypothesis 2a) Receivers with a high polygenic risk score (PRS) will:

1. have increased breast cancer anxiety compared to baseline in the short-term (2 weeks after receiving results), but these will return to baseline levels in the long-term (12 months after receiving results); and
2. be more likely to report having implemented risk-reducing strategies 12 months after receiving their results, compared to receivers with a low PRS.

Hypothesis 2b) Unaffected receivers with a low PRS will have decreased breast cancer anxiety 2 weeks after receiving results, which will be sustained at 12 months, compared to affected women who receive a low PRS.

 Hypothesis 2c) Affected women who receive a high PRS result will exhibit larger increases in breast cancer anxiety from baseline in the short-term (2 weeks after receiving results), compared to unaffected women who receive a high PRS.

**Aim 3.** Invite up to 40 receivers to participate in-depth, semi-structured telephone interviews and explore their experience receiving their genomic testing results.

**Aim 4.** Record all genetic counselling consultations associated with this research study at the Peter MacCallum Cancer Centre and Royal Melbourne hospital to explore factors associated with providing polygenic risk results.

# RESEARCH PLAN

## Study timeline.

The study duration will be from September 2015 to September 2018

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **2015** | **2016** | **2017** | **2018** |
| Annual quarter | **4th** | **1st** | **2nd** | **3rd** | **4th** | **1st** | **2nd** | **3rd** | **4th** | **1st** | **2nd** | **3rd**  |
| Questionnaire development, ethics applications  |  |  |  |  |  |  |  |  |  |  |  |  |
| Genetic counsellors training  |  |  |  |  |  |  |  |  |  |  |  |  |
| Staggered mail out of notification letters, recruitment and baseline data collection  |  |  |  |  |  |  |  |  |  |  |  |  |
| Follow-up data collection and telephone interviews  |  |  |  |  |  |  |  |  |  |  |  |  |
| Data analysis & manuscripts  |  |  |  |  |  |  |  |  |  |  |  |  |

## Number of centres

Participants will be recruited from the following centres:

**Peter MacCallum Cancer Centre**

Familial Cancer Centre

 305 Grattan Street Melbourne Victoria, 3000

**Royal Melbourne Hospital**

Familial Cancer Centre

Grattan St

Parkville

Victoria 3050

**Austin Hospital**

Clinical Genetics Service

145 Studley Rd

Heidelberg

Victoria, 3084

**Monash Medical Centre**

Familial Cancer Centre

246 Clayton Rd

Clayton

Victoria 3168

**Cabrini Hospital**

Family Cancer Clinic

181-183 Wattletree Road

Malvern

VIC 3144

**The Royal Hobart Hospital**

Clinical Genetic Service

48 Liverpool Street

Hobart

TAS 7000

## Participants

Approximately 400 women will be recruited to this study from the existing ViP cohort.

## Inclusion Criteria

Only women aged 18 years and over who are participating in the ViP study will be recruited into this evaluation. All families participating in the parent study will have already been tested for high-penetrance mutations in the breast cancer genes *BRCA1* and *BRCA2* and no such mutations have been identified.From this study population, women will be eligible to participate if they can provide their written informed consent and must indicate their willingness to participate and to comply with the study by reading, signing and returning the Participant Consent Form to the research assistant. Women must be sufficiently proficient in English to be able to complete the questionnaires.

Both index cases with a personal history of breast cancer and their family members (affected and unaffected) will be invited to participate in this psychosocial study. This study will include women with a low (N=200) and high (N=200) PRS. Each group will then stratified by disease status, such that about 100 affected and 100 unaffected women are included in each study group (Figure 2).

**Figure 2: Composition of ViP study (parent study) and Psychosocial Study sample**

ViP study (parent study):

- index cases and affected + unaffected relatives

Study sample:

200 women high PRS (100 affected + 100 unaffected)

200 women low PRS (100 affected + 100 unaffected)

Genetic testing:

*BRCA1/BRCA2* + common risk variants

**Low**

**PRS**

**20%**

Intermediate PRS 40%

**High**

**PRS**

**20%**

*BRCA1/BRCA2* or other high penetrance mutation 20%

Key: High PRS = high polygenic risk score; Low PRS = low polygenic risk score; affected = personal diagnosis of cancer; unaffected = no personal diagnosis of cancer; shaded area = sample eligible for psychosocial study

## Exclusion Criteria

Women where rare high-penetrance gene mutations have been identified will be excluded from the study, as will men, who constitute a very small proportion of index cases (<5%) and relatives (<10%). Men will be excluded from the study as the small sample size will preclude a meaningful statistical comparison with the majority female cohort. Women who receive an intermediate PRS will also be ineligible, because intermediate PRS results do not change a woman’s risk status and hence risk management advice in a clinically meaningful way.

Women whose primary language is other than English (LOTE) are eligible to participate in this research, provided they are sufficiently proficient in English to read study documentation and complete the evaluation questionnaires required as part of their participation in this study. The funding parameters for this project mean that it is not feasible to develop the study documentation and the assessment tools in multiple languages. Hence, women must be able to complete English language self-administered questionnaires to be eligible to participate in the study.

Patients with obvious intellectual or mental impairment that may interfere with the patient's ability to understand the requirements of the study will also be excluded.

## Questionnaire development and measures

Clinical data will be available through the ViP study including: number of affected first- and second-degree relatives, including number deceased due to breast cancer; personal history of breast cancer; and, for affected women, time since diagnosis.

Participants will be asked to complete up to three questionnaires depending upon their decision to receive or not receive their genomic testing results (Appendix O). Questionnaire 1 (Q1), is the baseline questionnaire and will be completed by all participants. Baseline data from Q1 will be compared between receivers and decliners to assess factors associated with uptake of genomic testing results. Q1 will include the following measures: M1 to M14 (Appendix B).

Questionnaire 2 (Q2) will only be completed by women who opt to receive their genomic testing results, ‘receivers’. Participants will complete Q2 two weeks after receiving their test results. The purpose of Q2 is to assess the short term psychological and behavioural impact of receiving one’s genomic testing result. Q2 will include the following measures: M4, M9 to M11 and M14 to M18 (Appendix C).

Questionnaire 3 (Q3) will be completed by both receivers and decliners. Q3 will assess the long term psychological and behavioural impact of receiving or not receiving one’s genomic testing result. Receivers will complete Q3 12 months after receiving their genomic testing result. Decliners will complete Q3, 12 months after enrolment in the psychosocial study. For receivers, Q3 will include M4, M9 to M14, M16 to M18 (Appendix D). Decliners will complete a shorter version of Q3 which will include M9, M10, M12 to M14, M16 and M19 (Appendix E).

The following measures have been selected for this study:

1. *Demographic characteristics –* including age, gender, country of origin, marital status, educational level, income, language spoken at home, number of biological children and previous attended at FCC.
2. *Protection motivation –* one 7-point Likert-type item will assess intention to receive result.
3. *Perceived severity* – will be assessed with one item to assess perceived severity of breast cancer [[16](#_ENREF_16)].
4. *Perceived vulnerability* – will be measured with three items to assess perceived risk of developing breast cancer [[18](#_ENREF_18)].
5. *Response efficacy –* will be measured using six items to assess perceived benefits of receiving genomic testing results [[18](#_ENREF_18)].
6. *Response cost –* will be measured using six items to assess perceived barriers to receiving genomic testing results [[18](#_ENREF_18)].
7. *Self-efficacy –* will be measured with seven items to assess confidence in undertaking variant testing despite ‘obstacles’ (e.g. family opposes) [[17](#_ENREF_17)].
8. Uncertainty *avoidance* – will be assessed using the eight item Attitudes towards Uncertainty scale [[19](#_ENREF_19)] which has previously demonstrated high internal reliability [[17](#_ENREF_17)].
9. *Breast cancer anxiety (fear) –* will be 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 [[20](#_ENREF_20), [21](#_ENREF_21)].
10. *Anxiety and Depression –* will be measured using the 14 items Hospital Anxiety and Depression Scale (HADS) [[22](#_ENREF_22)]. This is a widely used measure of emotional disturbance and has been demonstrated to have high internal reliability [[23](#_ENREF_23)].
11. *Knowledge* –10 true-false questions have been developed to assess knowledge of polygenetic risk and familial breast cancer.
12. *Stressful life events*: will be assessed using the 12-item List of Threatening Experiences, which measures common threatening life experiences, including serious illness and death in the family [[24](#_ENREF_24)]. Threatening life events may affect distress levels and will be measured as potential confounding variables.
13. *Concordance with screening guidelines* – women will be categorised in terms of their concordance with national guidelines for mammography and clinical breast examination [[25](#_ENREF_25)] screening using the approach used in a previous study [[26](#_ENREF_26)].
14. *Intention to take up and actual uptake of preventative strategies –* these include risk reducing surgery (bilateral mastectomy), medication (i.e. tamoxifen and raloxifen) and lifestyle factors (i.e alcohol consumption).
15. *Satisfaction with Information Provided –* participants will be asked to indicate how satisfied they were with the information provided by the genetic counsellor or geneticist at their results appointment on a 5 point Likert scale, with responses ranging from “very satisfied” (1) through to “very dissatisfied” (5). They will also be required to indicate whether the amount information received was “too much”, “about right” or “too little” and whether the language used was “too complicated”, “about right” or “too simple”.

Receivers will also complete the following additional measures at the two-week and 12 month follow up:

1. *Regret over the decision* – will be assessed using the 5-item Decision Regret Scale, which correlates with decisional conflict and quality of life [[27](#_ENREF_27)].
2. *Test related distress, positive experience and uncertainty-* Thisis a 19-item measure, assessing distress specifically in the context of genetic testing (e.g. ‘feeling upset about my genetic risk factor result’) and positive experiences (e.g. ‘feeling relieved about my genetic risk factor result’), uncertainty (e.g. ‘being uncertain about what my test result means about my cancer risk’) [[28](#_ENREF_28)].
3. *Recall and interpretation of testing results* – 3 items have been developed to assess recall and understanding of testing results.

Decliners will complete the following measure at the 12-month follow up:

1. *Reasons for declining results*– will be assessed with 15 items used in a previous [18]. Women will be asked to indicate the extent to which possible reasons for declining to receive results apply to them.

## Procedures and consent process

Women selected for inclusion in the sample will be invited by letter by the Melbourne-based Research Assistant (RA) (Appendix F). This invitation package will also include: Participant Information and Consent Form (Appendix G), response sheet (Appendix H), educational pamphlet on genomic testing and breast cancer risk (Appendix I), and reply paid envelope addressed back to the Melbourne RA.

In the response sheet participants will have an option to opt-out of this study. Those who opt-out will not be contacted further. Participants who do not return the response sheet two weeks after the invitation letters are sent will be contacted by the Melbourne-based RA. The RA will contact participation to confirm they have received the invitation package and find out whether they would like to take part in the study.

Women who consent to participate in the study will be sent Q1 by the Sydney-based study co-ordinator and provided with a telephone number to ring the study co-ordinator in case they have questions about the questionnaires. All those not returning Q1 after three weeks will be telephoned by the study co-ordinator to confirm they have received the questionnaire. Participants will have the choice of completing mailed or online questionnaires.

Twelve months after receipt of the initial invitation letter, participants who did not receive their genomic testing result will be asked to complete Q3. Reminder letters and phone calls will be made as appropriate by the research co-ordinator.

For participants who indicate that they wish to receive their genomic testing result, the Melbourne RA will contact the FCC through which families were ascertained originally to arrange for an appointment (Peter MacCallum Cancer Centre, Royal Melbourne Hospital, Monash Medical Centre, Austin Hospital or Cabrini Hospital). They will be asked to complete Q2 two weeks and Q3 12 months after receiving their test result (Figure 3).

At each participating FCC, at least one staff member will be trained in how to return PRS results. This will include training on: provision of information about polygenic risk, pre-test discussion of possible test outcomes and their impact on risk management options, implications for family members, and potential psychosocial implications. A report format for clinicians to use during genetic counselling consultations to communicate tailored results to patients, which incorporates graphical risk displays, has been developed in preliminary studies.

Data on FCC attendance and testing results will be ascertained through the participating FCCs. A brief consultation report (Appendix J) will be completed after participant attendance, which includes: test result, type of cancer (for affected women), recommended risk management strategies discussed, number of occasions of service, length of consultation, and health professionals involved in the consultation. The consultation report will trigger Q2 and Q3.

Consent will be sought from genetic health professionals at Peter MacCallum Cancer Centre and Royal Melbourne Hospital who have been invited to record their genetic counselling consultation as part of this study. The research assistant for the study will discuss this additional component of the research with the genetic health professionals to obtain their consent. Genetic health professionals who opt out of this part of the research (i.e. record their consultations) will still be eligible to participate in the return of polygenic results if they wish.

Figure 3: Flow of participants through the study

Invitation package sent

Q1

Attends FCC (receiver)

Does not attend FCC (decliners)

Q2

Q3

Q3

Interviews (up to 40 receivers)

Study decliners

0 days 2 weeks 4 weeks 12 months

Key: Q1 = baseline questionnaire; Q2 = 2 week questionnaire; Q3= 12 month questionnaire; FCC= Familial Cancer Clinic.

Consults recorded (2 sites)

## Semi-Structured Interviews

Up to 40 receivers will be invited by the study co-ordinator to participate in an in-depth semi-structured telephone interview (Figure 4). Selection criteria for this sub-study will include participants who attended a FCC to receive their genomic testing result. Participants will be grouped according to their PRS score (either high or low) and whether or not they had previously attended a FCC to discuss their personal risk for breast cancer. Participants who did not receive their test results will be excluded from this qualitative study. Participants will have an option to opt-out of this qualitative study in the consent form.

Interviews will be conducted by the research co-ordinator (T.Yanes) and will take place two weeks after participants received their test result. The interviews will be informed by a topic guide based on the literature and research questions (Appendix K). Topics explored will include: reasons for attending FCC, participants’ recollection of risk result, family communication and understanding, and changes to risk perception and risk management. Each interview should take approximately 30-60 minutes.

The transcribed interviews will be analysed for themes using an agreed set of codes. The qualitative analysis software NVivo will be used to categorise the data and facilitate comparisons. The study co-ordinator and principal investigators will participate in this process and agree upon emergent themes. Data analysis will take place concurrently with data collection, and results from each interview will be used to suggest additional lines of questioning in subsequent interviews to ensure that divergent points of view will be expressed.

Figure 4: Selection of participants for semi-structured interviews

40 “receivers” selected for semi-structured interview

20 received low PRS

20 received high PRS

Key: Receivers = participants who opted to receive their genomic testing result; PRS = polygenic risk score; FCC = family cancer clinic; ViP = Variance in Practice Study

10 did not attend FCC prior to enrolling in ViP study

10 did not attend FCC prior to enrolling in ViP study

10 attended FCC prior to enrolling in ViP study

t

10 attended FCC prior to enrolling in ViP study

## Recorded Genetic Counselling Consultations

All genetic counselling consultations associated with this research study at the Peter MacCallum Cancer Centre and Royal Melbourne Hospital will be recorded (Figure 3). The consultations will be transcribed and any identifiable information removed.

The transcribed consultations will be subjected to a rigorous communication behaviours analysis, using the quantitative methodology described by Lobb [[29](#_ENREF_29)]. It is anticipated that additional project funding will be sought to perform these analyses. As described by Lobb [[29](#_ENREF_29)] a detailed coding system and coding manual will be devised. The coder’s manual will enable standardisation of the coding procedure and facilitate calculation of inter-rater reliability. The transcripts will be coded to capture the main aspects of genetic counselling and will encompass the two broad categories of communication style and information-giving behaviours. The presence or absence of each main aspect of communication style (e.g. supportive or counselling behaviours) and information-giving (e.g. providing information on screening or prevention) component will be coded. Descriptive statistics will be used to summarise the data. Frequencies will be calculated for counselling behaviour. Total scores for the pre-defined counselling categories will be calculated by summing the component behaviours. Univariate analyses exploring associations between (a) demographic variables, psychological status, disease status (affected/unaffected) and consultation styles; and (b) patient outcomes (e.g. breast-cancer related anxiety, knowledge) will be undertaken, followed by multivariate analyses. These analyses will explore the effect of consultant communications on outcomes, controlling for potential confounders.

# Statistical Considerations

## Sample Size Calculation

Based on our pilot data where 62% of women invited participated in the study and opted to receive their results, we anticipate that about 400 women will need to be invited to the study. It is estimated this will result in 248 receivers for whom completed Q1 and Q2 will be available. Assuming a participation rate of 70% amongst women who decline receiving their results (estimated at 152), 106 decliners can be expected to complete both Q2 and Q3*,* based on asimilar study (P00006660). Thus the receivers group will include 62 affected with a low PRS and 62 affected women with a high PRS, and the same number of unaffected women with a low and high PRS. This sample size will have 80% power at a 5% significance level (2-sided) to detect a 0.5 effect size difference in breast cancer anxiety scores measured at the 2-week follow-up between affected and unaffected women who receive a high PRS (hypothesis 2c) as measured by the Impact of Event Scale (SD 10.0, [[30](#_ENREF_30)] range 0-75 scores), the primary outcome variable. This difference is a medium effect size using the convention by Cohen, [[31](#_ENREF_31)] and we consider it a clinically meaningful difference to detect [[32](#_ENREF_32)]. It is equivalent to 1 item (out of 15) endorsed as ‘Not at all’ instead of ‘Often’ (e.g. ‘I thought about breast cancer when I did not mean to’). Based on previous similar study where 13% loss to follow up at 12 months was observed (P01319455), we estimate 215 completed *Q*3 will be available.

## Quantitative Data Analysis

Data will be analysed using the SPSS program. Basic descriptive statistics, including means, medians, percentages, ranges and standard deviations will be calculated to describe the sample in terms of socio-demographic characteristics. The means of baseline key variables (M3 to M11) will be compared between receivers and decliners using independent samples t-test. Categorical data will be analysed by X2 test or Fisher’s exact test, as appropriate, whereas Student’s t-test for independent samples will be applied for continuous variables. Paired samples t–test will be applied to paired data of the baseline and follow up questionnaires. Equivalent non-parametric tests will used to analyse non-normally distributed data.

For each of the main outcome variables (M9 to M15), linear or logistic regression shall be used as appropriate. Further multivariate analyses will be used to adjust for potential confounding variables (e.g. age, parity, income). Appropriate regressions will be performed to investigate whether outcomes differ between receivers and decliners (hypothesis 1a) and between subgroups of affected and unaffected women (2c) and those receiving either a low or a high PRS (2a.ii). Repeated measurements will be analysed using linear mixed models to assess how outcomes change over time amongst receivers (hypothesis 2a.i and 2b) [[33](#_ENREF_33)]. This approach adjusts for the repeated measures per person and also allows for missing values. Logistic mixed models will be used if there is a need to dichotomise an outcome variable. Correlations between women in the same family cluster will also be adjusted via mixed models.

# STORAGE AND ARCHIVING OF STUDY DOCUMENTS

To ensure confidentiality and anonymity of all participants: all paper-based data will be stored in locked filing cabinets in the secure offices of the Psychosocial Research Group, Prince of Wales Clinical School throughout the project; all electronic participant data will be stored in password-protected computer databases during and after the project; each participant will be allocated a unique identification number, such that questionnaires and electronic data will not have any identifying information on them; consent forms will be stored securely and separately from questionnaire data in locked filing cabinets. Only the study coordinator and primary supervisor will have access to completed questionnaires and other research documents for the purposes of data analysis and the preparation of manuscripts.

After completion of the project, all paper copies of the data will be transferred to locked filing cabinets in a secure storage room location at the Psychosocial Research Group, UNSW, and a secure server at UNSW. Information will be stored for a minimum of seven years after publication of the final paper arising from the research, as required by Australian regulations and guidelines and then disposed of through shredding of paper based documents and erasure of electronic data. The study results will be reported in peer-reviewed journals and at relevant national and international meetings.

#  ETHICAL CONSIDERATIONS

The protocol for this study has been submitted for approval by the appropriate Human Research Ethics Committees at the recruitment centre. All participants will be provided with a written Informed Consent Form and an Information Pamphlet in which the study will be outlined clearly. Contact details for the study co-ordinator and relevant ethics committee(s) will also be provided to answer any questions or concerns participants may have. If a participant experiences any anxiety or distress as a consequence of this project, appropriate referrals will be arranged.

All participants will be made aware of their rights to access their own research results and the overall results in accordance with the National Statement on Ethical Conduct in Human Research. Participants will be informed about how the results will be disseminated, including how they will be published and presented to the broader scientific community and the public. Accountability to participants for the aggregated results of the research will be addressed through open disclosure and sharing of ideas about research issues. Throughout the research, participants will be encouraged to contact the study co-ordinator to discuss the results and to address any questions or concerns they may have. Any complaints relating to the research will be comprehensively recorded and addressed in accordance with the relevant Human Research Ethics Committee policy.

At research completion, a lay summary of the study findings (de-identified) will be prepared and sent to all those participants, who previously indicated that they wished to receive a copy. Results will be presented to the scientific community at national and international conferences and in peer-reviewed journal publications.

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# APPENDICES

List of appendices that accompany this protocol:

1. Questionnaire 1
2. Questionnaire 2
3. Questionnaire 3 receivers
4. Questionnaire 3 decliners
5. Invitation Letter
6. PICF
7. Response Sheet
8. Educational Pamphlet
9. Consultation Report
10. Interview Guide
11. Cover letter for Questionnaires
12. Study Flow Chart
13. Withdrawal of Participation
14. Summary of measures and questionnaires
15. Protocol: Common genetic variants and breast cancer risk (HREC/11/PMCC/43)
16. PICF Genetic Health Professionals
17. Notification of study enrolment closing
18. GHP Demographic Questions