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Evaluation of two population screening programmes for *BRCA1/2* founder mutations in the Australian Jewish community: a protocol paper

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ABSTRACT

Introduction People of Ashkenazi Jewish (AJ) ancestry are more likely than unselected populations to have a *BRCA1/2* pathogenic variant, which cause a significantly increased risk of breast, ovarian and prostate cancer. Three specific *BRCA1/2* pathogenic variants, referred to as *BRCA*-Jewish founder mutations (B-JFM), account for >90% of *BRCA1/2* pathogenic variants in people of AJ ancestry. Current practice of identifying eligible individuals for *BRCA* testing based on personal and/or family history has been shown to miss at least 50% of people who have one of these variants. Here we describe the protocol of the JeneScreen study—a study established to develop and evaluate two different population-based B-JFM screening programmes, offered to people of Jewish ancestry in Sydney and Melbourne, Australia.

Methods and analysis To rmeasure the acceptability of population-based B-JFM screening in Australia, two screening programmes using different methodologies have been developed. The Sydney JeneScreen programme provides information and obtains informed consent by way of an online tool. The Melbourne JeneScreen programme does this by way of community sessions attended in person. Participants complete questionnaires to measure clinical and psychosocial outcomes at baseline, and for those who have testing, 2 weeks postresult. Participants who decline testing are sent a questionnaire regarding reasons for declining. Participants with a B-JFM are sent questionnaires 12-month and 24-month post-testing. The questionnaires incorporate validated scales, which measure anxiety, decisional conflict and regret, and test-related distress and positive experiences, and other items specifically developed or adapted for the study. These measures will be assessed for each programme and the two population-based B-JFM screening methods will be compared.

Ethics and dissemination Institutional Human Research Ethics Committee approval was obtained from the South Eastern Area Health Service Human Research Ethics Committee: HREC Ref 16/125.Following the analysis of the study results, the findings will be disseminated widely through conferences and publications, and directly to participants in writing.

Strengths and limitations of this study

- JeneScreen is using population-based methods to efficiently identify individuals in the Jewish community with a BRCA-Jewish founder mutations and thus who are at increased risk of breast, ovarian and prostate cancer, irrespective of family history.
- The study will also provide valuable evidence to guide the development of future programmes, which offer broader population-level genetic testing for individual disease risk.
- Through identification of individuals with *BRCA1/2* pathogenic variants, JeneScreen enables cascade testing in a clinical setting of at-risk relatives of participants identified with cancer-predisposing genetic variants, further enhancing its public health impact.
- The study design allows for prospective data collection, enabling comparison of data both between participants and in individuals over time.
- Eligibility is limited to residents of Sydney and Melbourne, although study findings will assist with the development of a programme to be offered to all Australians of Jewish ancestry.

INTRODUCTION

Three *BRCA1/2* pathogenic variants, *BRCA1* c.68_69delAG (p.Glu23ValfsTer17), *BRCA1* c.5266dupC (p.Gln1756Profs), and *BRCA2* c.5946delT (p.Ser1982ArgfsX22) are referred to as *BRCA1/2* Jewish Founder Mutations (B-JFM). One of the three B-JFMs are present in approximately 2.5% of people of Ashkenazi Jewish (AJ) ancestry,[1 2] compared with an estimated prevalence of *BRCA1* and *BRCA2* pathogenic variants of 0.3% in the general population.[3] B-JFM are inherited in an autosomal dominant manner. B-JFM account for >90% of *BRCA1/2* pathogenic variants in people of AJ ancestry[4] and cause approximately 12% of all breast cancer[5] and approximately 35% of all ovarian cancer in people of

AJ ancestry.[6] Pathogenic variants in *BRCA1* are associated with a 72% risk of female breast cancer and a 44% risk of ovarian cancer up to age 80 years.[7] The risk for female breast cancer is similar for *BRCA2* (69%) and lower for ovarian cancer (17%),[7] but higher risks for breast cancer (~7%) and prostate cancer (>15%) are observed for males with a mutation in *BRCA2* compared with males with a mutation in *BRCA1*.[8–10] There is evidence that *BRCA2* c.5946delT falls in a region which may be associated with a relatively lower risk of breast cancer and higher risk of ovarian cancer compared with other *BRCA2* mutations, however, the absolute mutation specific risks are imprecise and do not change guidelines for management.[11]

Until now, B-JFM testing has generally only been offered to individuals of AJ ancestry in Australia with a personal or family history of breast and/or ovarian cancer, as currently recommended by the Australian guidelines for BRCA1 and BRCA2 testing, through eviQ.[12] However, a family history of cancer is not always present or known, and this is particularly an issue for families of Jewish ancestry due to the impact of the Holocaust and family dispersal from migration.[13] Previous studies show that over half of individuals with a B-JFM identified through population screening do not have a personal or family history of cancer.[14–16] Without this history, individuals may not meet the current Australian guidelines for B-JFM testing.[12] The implication is that at least half of people with a B-JFM in Australia must wait for a personal or family member's cancer diagnosis before they are eligible to undergo testing and be informed of their genetic risk.

According to 2016 census data, the Australian Jewish population numbered almost 118 000 people.[17 18] This number reflects only those Australians who completed the census and self-identified as Jewish in an 'other religion' category, so it likely underrepresents the true number of individuals who are at risk due to their Jewish ancestry. Based on the prevalence set out above, it is expected that approximately 2000–2500 Jewish people have a B-JFM in Australia. There is an urgent need for new approaches to identify unaware at-risk members of the community, to offer early detection and risk reduction strategies. With the cost of genetic testing declining sharply, there is an opportunity to implement population-wide genetic screening for all Australians of Jewish ancestry who wish to have such testing. Census data showed that 46% of the Australian Jewish population live in the state of Victoria (of which Melbourne is the capital city), and 41% live in New South Wales (of which Sydney is the capital city).[18] This means that Melbourne and Sydney are the best candidates for recruitment for a pilot study of population-wide screening.

Testing all individuals of Jewish ancestry for B-JFM through population screening has been advocated in Canada, UK and Israel,[14–16 19–24] and satisfies the principles for population screening for genetic susceptibility[25–28] as well as the original WHO criteria for screening.[29] B-JFM testing identifies carriers who can then undergo regular surveillance for early cancer detection[30] and preventative surgical procedures[31] to decrease cancer morbidity and mortality and significantly improve health outcomes in this population.[32] Previous B-JFM population screening programmes have successfully identified a larger number of individuals with a B-JFM than standard clinical practice.[15 33] High satisfaction and acceptability was seen among these B-JFM population screening participants.[15 16 21] This evidence supports the implementation and evaluation of a B-JFM population screening programme for the Australian Jewish population. The programmes implemented in other countries have differed in participant eligibility and methods of pretest and post-test information provision. Some programmes were specifically for males or females, but not both. There has been variation in Jewish identity, both in the number of Jewish grandparents required for eligibility, and whether they were Ashkenazi. To our knowledge neither an online clinical B-JFM programme, nor screening after group pretest education sessions have been implemented and assessed.

The current model of pretest face-to-face counselling carried out in familial cancer clinics (FCCs) in Australia is time-intensive and cost-intensive and unlikely to be financially sustainable for a population screening programme.[13 21] For population-scale genetic screening to be feasible, innovative methods for achieving efficiency, while still delivering the education and support required, must be developed. These include more cost-effective methods of pretest and post-test education and counselling, both for individuals with pathogenic variants and those with a moderate to strong family history of breast and/or ovarian cancer.[19]

Previous studies in Australian Jewish communities have demonstrated the acceptability of population carrier screening programmes for recessive genetic conditions commonly found in the AJ population.[34–37] A study exploring the attitudes of 370 members of Sydney's Jewish community found that over 90% were supportive of a B-JFM population screening programme, and more than 60% were interested in having B-JFM testing through a population screening programme.[38] Almost half were aware of a family history of breast or ovarian cancer; however, over 70% of these people had not undergone *BRCA1/2* testing.[38]

Aims

The JeneScreen study aims to evaluate and compare two models of population-based B-JFM testing programmes for the Jewish communities in Sydney and Melbourne.

The programmes in Sydney and Melbourne incorporate key methodological differences: online education and consent in Sydney compared with face-to-face group education in Melbourne. The acceptability of these programmes will be assessed and compared through satisfaction measures. The education provided will be assessed with knowledge, anxiety, perceived risk and decisional conflict/regret scales. Beyond the potential health benefits to participants and their relatives, JeneScreen's findings will generate valuable evidence regarding if and how

such testing should be offered. It will inform the development of future population-level genetic screening initiatives, not only for B-JFM, but also for testing programmes for genes in which variants cause other preventable disorders, such as cardiac conditions.

METHODS AND ANALYSIS

Inclusion and exclusion criteria

Inclusion criteria:

- Age ≥18 years old.
- Has at least one Jewish grandparent (does not have to be AJ).
- Currently resides in Sydney or Melbourne.
- Can read and communicate in English.

Exclusion criteria:

- Has previously undergone *BRCA1/2* testing.
- Is aware of a family member who has been identified as having a *BRCA1/2* mutation.
- Has been diagnosed with cancer within 12 months prior to participating in the study (other than non-melanoma skin cancer).

The programme is open to both men and women. Men are encouraged to participate, in order to identify at-risk female relatives and provide male carriers with surveillance and reproductive options. People who are aware of a family member with a *BRCA1/2* mutation require a more personalised consultation in an FCC for predictive testing than is offered through the online process in Sydney or the community presentation made in Melbourne. Therefore, these individuals are offered an appointment at an FCC.

Sydney programme

Pretest information

The Sydney programme (figure 1) uses an interactive online information tool to deliver pretest information to participants and to enable participants to provide online consent. The online information tool was developed largely by LA, who is the head of the Hereditary Cancer Clinic at Prince of Wales Hospital, Sydney. The online tool provides all information and addresses issues usually discussed during a pre-test, face-to-face consultation, and includes links to external sources of additional information. The online tool was reviewed and approved by the steering committee during its development. Eligible participants work through the tool at their own pace, in their own time, and can contact a genetic counsellor for further information and assistance at any time throughout the process.

Consent

Participants are asked to read through the online information. Following this, those who decide to have B-JFM testing provide online consent for testing. Both those deciding to have testing and those who decline testing then complete the baseline questionnaire (Q1).

DNA collection

Participants who consent to the test are posted a buccal swab DNA collection kit, along with instructions, and a reply-paid envelope.

Result delivery

Participants receive results through either a face-to-face consultation with a genetic clinician and genetic counsellor or by email. The majority of B-JFM negative

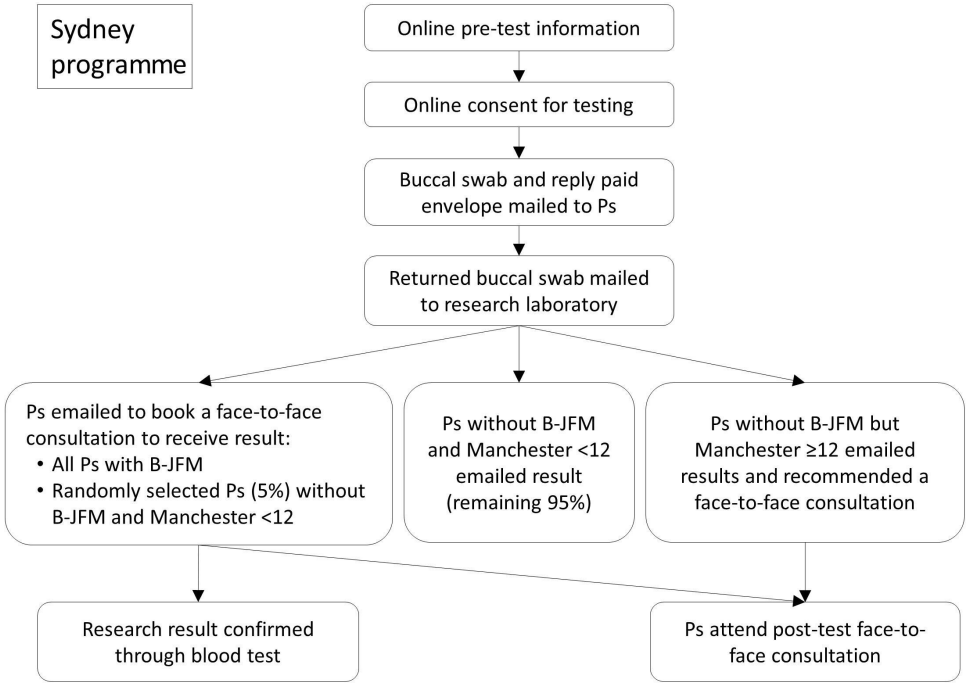

Figure 1 Sydney JeneScreen programme. B-JFM, BRCA-Jewish founder mutations; P, participant.

participants receive their results through an email. Participants with a B-JFM and a randomly selected 5% sample of those without a B-JFM receive an email offering an appointment for a face-to-face consultation at the Hereditary Cancer Clinic at Prince of Wales Hospital. This ensures that participants invited to a face-to-face consultation do not know whether they have a B-JFM prior to the consultation and enables comparison with telephone results.

During the face-to face consultation, participants with B-JFM are provided with information regarding options for preventive action, screening recommendations and reproductive options (if applicable). Predictive testing of family members is discussed and arranged if applicable.

The self-reported personal and family history of cancer in the baseline questionnaire (Q1) is used to calculate a Manchester Score (MS) for each participant. The MS system is a validated tool[39] to calculate the probability that a non-Jewish individual carries a pathogenic variant in *BRCA1* or *BRCA2* (12). As there are no validated tools for risk assessment of Jewish individuals who do not carry a B-JFM, this study uses a MS of ≥12 (indicating a 3% chance of carrying a mutation) to identify B-JFM negative participants whose family history could be clinically significant and warrants offer of a formal genetics referral.

Participants without a B-JFM but with MS ≥12 receive their results by email and are invited to attend a face-to-face consultation with the genetic clinician and genetic counsellor. During that consultation, the participant's cancer risk, as well as possible further testing and risk management options, are discussed. Individuals without a B-JFM who have MS <12 (other than the 5% randomly selected to be invited to a face-to-face consultation) receive their results by email.

Melbourne programme

Pretest information

The Melbourne programme (figure 2) provides pretest information to participants by way of community presentations. A genetic counsellor delivers the presentation in person. Where the event is stand-alone for the JeneScreen programme, participants are required to pre-register and up to 120 participants can attend each session. Where the event is held for another purpose and JeneScreen testing is offered to people attending the event, preregistration is not required. The presentation contains the same information provided to Sydney participants through the interactive online tool and takes approximately 20 min. Following the presentation, participants are invited to ask questions. Participants with personal questions can speak privately with the genetic counsellor after the presentation concludes. This approach is similar to that used in the autosomal recessive carrier testing programmes currently or previously offered to Jewish high school students in Sydney and Melbourne[34–37] and in two haemochromatosis screening studies, one in the workplace and one in high schools.[40 41] All participants are asked to complete a hard-copy version of the baseline questionnaire (Q1) immediately following the presentation.

DNA collection

Participants can provide a DNA sample through a buccal swab at the community presentation or take the buccal swab home and post it back at a later date using a reply-paid envelope.

Consent

Participants who are tested at the community presentation provide written consent with their DNA sample. Participants who take a swab home with them to post back

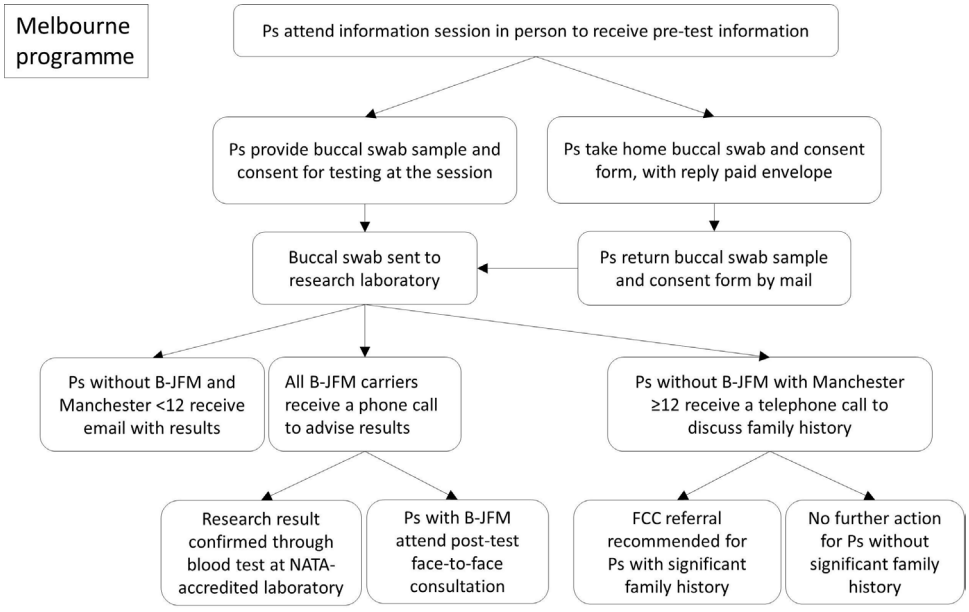

Figure 2 Melbourne JeneScreen programme. B-JFM, BRCA-Jewish founder mutations; FCC, familial cancer clinic; NATA, National Association of Testing Authorities; P, participant.

at a later date also take home the written consent form and include it in the reply-paid envelope when posting back the DNA sample.

Result delivery

Participants with a B-JFM receive results through a telephone call. During the call, they are invited to attend a face-to-face consultation, usually within a week. At that consultation, the genetic counsellor and clinical geneticist provide participants with preliminary information regarding risk reduction, screening and reproductive options (if applicable). The Melbourne programme is not conducted through an FCC. For that reason, following this appointment, participants are referred to an FCC for ongoing risk management and cascade predictive testing of at-risk relatives.

Melbourne participants without a B-JFM but MS ≥12 receive a telephone call from a genetic counsellor to discuss their result and their family history of cancer. The participant's family history is then assessed by a clinical geneticist to determine whether a referral should be made to an FCC for further risk assessment and advice. Participants without a B-JFM and MS <12 receive results by email. Participants can contact the coordinating genetic counsellor with enquiries or to access further support.

Recruitment

JeneScreen is advertised to the Jewish communities in Sydney and Melbourne through a dedicated website (www.jenescreen.com.au); articles in Jewish newspapers (paper and online); advertisements placed in newsletters of Jewish organisations, synagogues and schools; emails from community organisation databases; brochures handed out at community events; information provided by healthcare professionals; presentations at community events; and through social media. Recruitment is highly targeted and details are shared through communities, family members and by word of mouth. Participants in a previous Sydney-based study[38] who indicated interest in participating were also emailed an invitation to participate. In Melbourne, some events take place in Jewish synagogues and other community meeting places. Events are advertised through the Rabbi or other community groups involved with hosting the event.

Testing

Testing for the B-JFM is carried out as a research test by the Cancer Genetics Laboratory at the Peter MacCallum Cancer Centre, Melbourne. The DNA from the buccal swabs is extracted with the proteinase K DNA extraction method, followed by batch testing with high resolution melting (HRM) method to detect any variants in the targeted sequence. The results of any samples identified to have a B-JFM by HRM are validated by Sanger sequencing. All participants identified as having a B-JFM undergo clinical confirmation testing using a blood sample through a clinically accredited laboratory.

Outcome measures

Up to four questionnaires are completed by participants at different time points throughout the study (figure 3). These include soon after receiving pre-test information (Q1), 2 weeks after receiving results for those who undergo testing (Q2), 1 and 2 years after receiving results for those with a B-JFM (Q3 and Q4, respectively), as well as a questionnaire designed for those who decline testing (Decliners' Q). All of these questionnaires are completed online through Research Electronic Data Capture,[42] except for Q1 for participants in the Melbourne programme.

Questionnaire design

The questionnaires completed by participants collect demographic information and assess other outcome measures. Demographic information collected includes age, sex, relationship status, age and gender of children, level of education, level of medical training (if any), employment situation, number of Jewish grandparents and self-identification as AJ and/or Sephardic Jewish. The outcome measures assessed through the different questionnaires are outlined in table 1. The questionnaires incorporate validated scales, which measure anxiety, decisional conflict and regret and test-related distress and positive experiences. Other items specifically developed or adapted for this study are also included in

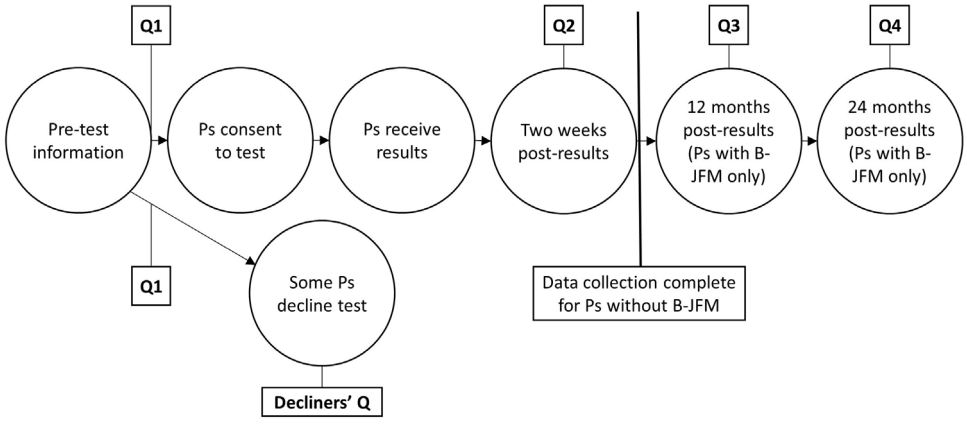

Figure 3 Questionnaires completed by participants. B-JFM, BRCA-Jewish founder mutations; P, participant.

Table 1 Summary of data collected and outcome measures assessed through questionnaires completed by participants

Measure	Q1 (post education/ preresults)	Decliner's Q (decliners of testing only)	Q2 (post results)	Q3 (12 months follow-up- *B-JFM* only)	Q4 (2-year follow-up- *B-JFM* only)
Demographics	✓				
Personal history of cancer[43]	✓				
Family history of cancer[43]	✓				
Knowledge[43–45]	✓		✓	✓	✓
Spielberger State-Trait Anxiety Inventory- six item[46]	✓		✓	✓	✓
Perceived risk of having a *BRCA1/2* mutation	✓				
Perceived risk developing breast cancer (women only)	✓		✓	✓	✓
Perceived risk of developing ovarian cancer (women only)	✓		✓	✓	✓
Perceived risk of developing prostate cancer (men only)	✓		✓	✓	✓
Decisional Conflict Scale[47 48]	✓				
Intention to undergo testing	✓				
Satisfaction with the genetic testing programme			✓		
Decision Regret Scale[49]		✓	✓	✓	✓
Test-Related Distress and Positive Experiences from the Multidimensional Impact of Cancer Risk Assessment Questionnaire[50]			✓	✓	✓
Reasons for declining the test[51]		✓			
Testing of family members of participants with B-JFM			✓	✓	✓
New personal or family cancer diagnoses for participants with a B-JFM				✓	✓
Uptake of screening and cancer risk reduction options by participants with a B-JFM				✓	✓

B-JFM, BRCA-Jewish founder mutations.

the questionnaires. The questionnaires contain material that cannot be reproduced online for copyright reasons, but copies can be requested from the authors.

The details of the specific outcome measures are also described below.

- Personal/family history of cancer is measured using a questionnaire developed for a previous study[43] which asks about personal and family history of breast, ovarian and prostate cancer.
- Knowledge is measured through questions specifically developed for this study and based on the understanding required to make an informed decision to undergo *B-JFM* testing. These questions were adapted for this study from previously validated questionnaires.[43–45]
- Anxiety is measured using the Spielberger State-Trait Anxiety Inventory (STAI).[46]
- The following self-reported perceived lifetime risks are measured on a numerical differential scale ranging from 0 ('no chance') to 100 ('definitely'):
  - Participants' perceived risk of having a B-JFM.
  - Female participants' perceived lifetime risk of developing breast and ovarian cancer.
  - Male participants' perceived lifetime risk of developing prostate cancer.
- Participants rate their perceived chance of having a B-JFM compared with the average person, and male and female participants rate their perceived risk of developing prostate cancer or breast and ovarian cancer, respectively, compared with the average person, using a 5-point Likert scale.
- Intention to undergo testing is measured through questions which ask directly about intent on undergoing testing at the present time and in the future.
- Decisional conflict is measured through a modified version of a validated 5-point Likert scale,[47 48] worded specifically for people making decisions about B-JFM testing. It measures personal perceptions of uncertainty regarding a decision; modifiable factors contributing to uncertainty; effective decision making likely to be implemented and satisfaction with choice.
- Satisfaction with genetic testing is measured through a 5-point Likert scale designed for this study. Participants who are dissatisfied with any component of the programme are also given an opportunity to elaborate using free text.

- Decisional regret is measured using the Decisional Regret Scale,[49] a validated 5-point Likert scale measuring regret following healthcare decisions.
- Test-related distress and positive experiences are measured using 10 items from a validated questionnaire (the Multidimensional Impact of Risk Assessment Scale).[50] Six items measure distress and four items measure positive experiences relating to genetic testing.
- Reasons for declining the B-JFM test are measured using the decliner's questionnaire, which was modified from a questionnaire previously used to assess reasons for declining a genetic counselling session to discuss genetic testing.[51]
- Family members tested and cancer diagnoses are measured through direct questions regarding whether any family members have undergone testing or whether there have been any new personal or family cancer diagnoses since the participant with a B-JFM received their results.
- Uptake of screening and cancer risk reduction options for participants with a B-JFM are measured through a questionnaire containing questions specifically designed for this study regarding uptake of screening tests (men and women), preventative surgery (women) and/or tamoxifen (women) and future plans to undertake preventative measures.

These measures will be assessed for each programme and the two programmes will be compared, to determine and compare acceptability of both population-based B-JFM screening and different methodologies. Other outcome measures being collected include the uptake of testing by participants and the proportion of participants with a B-JFM. The demographics of the two populations will be compared with determine if this has any influence on the outcome measures.

Patient and public involvement

A steering committee in Sydney, consisting of genetics professionals, 2 Rabbis and 10 lay members of the Sydney Jewish community, was established at the conception stage of the project. The committee was consulted and provided feedback on the project plan, as well as the online tool through surveys, before it was opened to the public. Key members of the Melbourne Jewish community, including Rabbis, genetics professionals and lay individuals provided guidance and contributed to the development of the Melbourne programme. Approximately 20 members of the Melbourne Jewish community participated in a pilot information session. The feedback they provided was incorporated into the Melbourne programme sessions.

Sample size

The study will compare the intervention in Sydney and the intervention in Melbourne. With a minimum number of 600 participants in each intervention group, the study will have 90% power to detect a 0.2 effect size. That is, for each of the outcome instruments, a difference of 0.2 of an SD between the mean scores for each intervention will be detected. This corresponds to a reasonably small effect size.[52]

Data analysis plan

An initial examination of the correlation matrix of the items of scales Speilberger STAI, Decisional conflict scale, Decision Regret Scale, Test-Related Distress and Positive Experiences and Decliner's questionnaire will be analysed to eliminate outliers and unrelated items. Normality assumptions of all remaining items using kurtosis and skewness scores will be checked. Parallel analyses will be used to determine the number of components to retain in an exploratory factor analysis of all scales which use multiple items. Principal component analysis with oblimin rotation will be used to examine item loadings and to explore the dimensionality and internal consistency of the scales. Reliability analyses will be undertaken based on Cronbach's alpha.

A descriptive statistical analysis will be carried out to summarise the data collected from all questionnaires. The means of all continuous outcome variables will be calculated. In univariate analysis continuous data will be compared using independent samples t-test between two independent groups for example, acceptors and decliners. Continuous data on same individuals will be compared using paired samples t-test. Similarly, independent and paired categorical data will be compared using Pearson's χ^2 and McNemar tests, respectively. Analysis of variance test will be used to compare if there are more than two categories of independent data. Non-parametric counterparts of these tests will be used whenever data is not normally distributed.

Multiple linear regression will be used for continuous outcome variables and logistic regression for the recoded binary outcome variables. All regression models will include the group variable, the baseline score of the outcome variable being tested, and the following potential confounding variables: age, level of education, cancer status and family risk status. For linear regression models, residuals will be checked for normality, and for logistic regression, Lemeshow and Homer's goodness of fit test will be calculated. Thorough checks to ensure the robustness of the model will be performed including variance inflation factor to assess collinearity, standardised residuals to detect and evaluate outliers and Cook's distance to identify influential cases. Logarithmic transformation will be performed to variables which are not normally distributed. Variables showing multicollinearity will be excluded from the model. A threshold p value of 0.20 will be used, and variables meeting this threshold in the univariate analysis will be entered in the logistic regression model. Linear mixed models will be used to analyse longitudinal data adjusting for missing data due to attrition.

ETHICS AND DISSEMINATION

Institutional Human Research Ethics Committee approval has been obtained from the South Eastern Area Health Service Human Research Ethics Committee: HREC Ref 16/125, and governance approval has been obtained for the Sydney (Prince of Wales Hospital) and Melbourne (Royal Children's Hospital) sites. Recruitment commenced in 2018 and is ongoing.

The administration of questionnaires presents no risks to study participants. However, providing genetic testing through online pre-test information or group presentations, rather than individual face-to-face consultations, may result in increased levels of distress for participants. Self-reported anxiety levels are monitored through participant questionnaires. Any participants reporting severe anxiety are followed up at this time and further support is offered as required. Participants can contact the investigators at any time if they have any concerns or are experiencing anxiety, with contact details provided through participant information forms and other study correspondence. All participants with a B-JFM receive usual genetic counselling care through an FCC. Consultation with a genetic counsellor, clinical geneticist and/or psychologist is arranged if necessary for any participant.

Following the analysis of the study results, the findings will be disseminated widely through conferences and publications, and directly to JeneScreen participants in writing.

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Contributors NEC, JT, BM, KB-S, RK, AB, LB, CJ, PAJ, AT, SN, MBD and LA were involved in conception and/or design of aspects of the study. NEC and JT are also responsible for implementing the protocol, data acquisition and drafting. MBD and LA are also responsible for critical revision of the work. IGC, SM and Y-AK are involved with lab protocol development and data acquisition.

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