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Population-based *BRCA1/2* testing programs are highly acceptable in the Jewish community: Results of the JeneScreen study

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ABSTRACT

Background

Ashkenazi Jewish (AJ) people have a higher incidence of *BRCA1/2* pathogenic variants (PV) than unselected populations. Three *BRCA*-Jewish founder mutations (B-JFM), comprise >90% of *BRCA1/2* PV in AJ people. Personal/family cancer history-based testing misses ≥50% of people with B-JFM.

Methods

We compared two population-based B-JFM screening programs in Australia – using 1) an online tool (Sydney) and 2) in-person group sessions (Melbourne).

Results

Of 2167 Jewish people tested (Sydney n=594; Melbourne n=1573), 1.3% (n=28) have a B-JFM, only 2 of whom had a significant cancer family history (Manchester score ≥12). Pre-test anxiety scores were normal (mean 9.9+/-3.5[6-24]), with no significant post-result change (9.5+/-3.3). Decisional regret (mean 7.4+/-13.0[0-100]), test-related distress (mean 0.8+/2.2,[0-30]) and positive experiences (reverse-scored) (mean 3.4+/-4.5,[1-20]) scores were low, with no significant differences between Sydney and Melbourne participants. Post-education knowledge was good overall (mean 11.8/15(+/-2.9)), and significantly higher in Melbourne than Sydney. Post-result knowledge was the same (mean 11.7 (+/- 2.4) versus 11.2 (+/- 2.4). Participants with a B-JFM had higher post-result anxiety and test-related distress and lower positive experiences, than those without a B-JFM, but scores were within the normal range. Family cancer history did not significantly affect knowledge or anxiety, or pre-test perception of B-JFM or cancer risks. Most participants (93%) were satisfied/very satisfied with the program.

Conclusion

Both B-JFM screening programs are highly acceptable to Australian Jewish communities. The program enabled identification of several individuals who were previously unaware they have a B-JFM, many of whom would have been ineligible for current criteria-based testing in Australia.

What is already known on this topic

Certain BRCA1/2 pathogenic variants are more common in Ashkenazi Jewish people than in the general, unselected population, and current methods for determining who should be tested fail to identify a large percentage of at-risk Jewish people. The acceptability of various methods of implementing population-based DNA screening has not been tested in the Australian Jewish population.

What this study adds

We found that both online and in person methods of offering DNA screening to the Australian Jewish population were highly acceptable.

How this study might affect research, practice or policy

Population-based DNA screening programs are becoming accepted internationally as a mechanism for identifying previously unaware, at-risk members of society. Our findings provide evidence about the acceptability of various methodologies for implementing population-based screening programs.

INTRODUCTION

The *BRCA1/2* Jewish founder mutations (B-JFM) (*BRCA1*:c.68_69delAG [p.Glu23Valfs*17]; *BRCA1*:c.5266dupC [p.Gln1756Profs*74]; and *BRCA2*:c.5946delT [p.Ser1982Argfs*22]) account for >90% of *BRCA1/2* pathogenic variants (PVs) in people of Ashkenazi Jewish (AJ) ancestry[1]. Approximately 2.5% of AJ individuals have a B-JFM[2], about eight times higher than in the general population, where the estimated *BRCA1/2* PV prevalence is 0.3%[3]. Females with a *BRCA1/2* PV have a ~70% risk of developing breast cancer and a 17-44% risk of ovarian cancer by age 80 years[4]. Males with a *BRCA1/2* PV have higher risks for prostate cancer (9-15%) and breast cancer (*BRCA1* 1.2%, *BRCA2* 7%)[5-7]. The impact of these cancer risks can be mitigated through regular surveillance for early cancer detection[8], as well as risk-reducing medication or surgery such as bilateral mastectomy and salpingo-oophorectomy[9].

Until now, B-JFM testing has generally only been offered through genetics services to Jewish Australians with a personal or family history of breast/ovarian/prostate/pancreatic cancer that meets established criteria[10]. However, family cancer history in Jewish individuals is often unknown, for reasons including the impact of the Holocaust and family dispersal from migration[11]. Previous international research shows that over half of AJ individuals identified with a B-JFM through population screening have no known personal or family cancer history[12-14]. It is likely that a similar number of Australian AJ individuals with a B-JFM are ineligible for current testing and will remain unaware of their personal risk until a personal or family cancer diagnosis. International B-JFM population screening programs have identified a significantly greater number of individuals with a B-JFM than standard clinical testing[13 15]. Offering population-level B-JFM screening to all individuals of Jewish ancestry is advocated in Canada, UK and Israel[13 14 16]. Given the known cancer risks and benefits of interventions, B-JFM testing satisfies the criteria for population-level genetic screening[17 18].

Previous Australian studies have demonstrated the acceptability of population carrier screening programs for autosomal recessive conditions in Jewish communities[19-21]. A study of 370 members of the Sydney Jewish community found that although 40% of participants had a family history of breast/ovarian cancer, <30% of those with a relevant family history had undergone *BRCA1/2* testing[22]. Over 90% of these participants were supportive of, and >60% were interested in having B-JFM testing through a B-JFM population screening program[22]. The high satisfaction demonstrated through international B-JFM population screening programs[13 14 23] further supports the evaluation of a B-JFM population screening program for the Australian Jewish population.

To be feasible, B-JFM screening must be time and resource efficient, without sacrificing necessary educational and support elements. The current clinical practice of providing individual face-to-face counselling before genetic testing is not sustainable for population-level screening[11], and various studies have investigated alternative service delivery models[24 25]. High acceptability and knowledge retention have been demonstrated in comparative studies of group vs individual face-to-face genetic counselling[26-29]. A scoping review found that across comparative studies, both group and individual genetic counselling resulted in high satisfaction levels, decreased anxiety, decreased decisional conflict and increased knowledge, although some preferences for access to individual counselling remained[24].

There is little research regarding outcomes of providing pre-test information and obtaining consent via online/web-based methods alone. A qualitative study of 11 early participants of the JeneScreen study demonstrated satisfaction with the online testing process[30]. Previous studies showed that computer-based tools designed to assist with the provision of pre-test information in addition to genetic counselling can reduce the resource burden of genetic counselling, although participants also preferred to have engagement with a genetic counsellor for individual questions, and individual

genetic counselling was still recommended for individuals at high risk[31-33]. A randomised trial comparing in-person provision of genomic risk information with online information provision[34] found in-person provision of information increased comprehension significantly. Further assessment of different ways of presenting results online to promote comprehension was recommended. In a study where computer-based decision aids (followed by genetic counselling) were compared with standard in-person genetic counselling, anxiety levels were similar in each group[33]. Anxiety did not decrease after computer use alone, but decreased after genetic counselling in each group

To our knowledge, no studies comparing the outcomes of offering genetic screening through an online program with large in-person group pre-test sessions, have previously been reported. In this study we compared the outcomes (including anxiety, decisional conflict, knowledge and satisfaction) of offering screening through an online portal with offering screening through in-person group sessions.

METHODS

The JeneScreen methodology has been published [35]. We offered B-JFM testing to Jewish residents of Sydney and Melbourne with at least one Jewish grandparent, at least 18 years of age, no previous *BRCA1/2* genetic testing history, no known blood relatives with a *BRCA1/2* mutation, and no personal cancer diagnosis (other than non-melanoma skin cancer) in the year prior to enrolment. The Peter MacCallum Cancer Research Laboratory conducted molecular B-JFM testing[35].

Recruitment

JeneScreen was advertised online through a website, social media, community organisations and health professionals. The study partnered with local synagogues, schools and other trusted organizations to promote the study and host recruitment sessions.

Data collected and outcomes assessed

Participants completed questionnaires at various time points, to measure a range of outcomes[35]: ***Questionnaire 1 (Q1) -*** after receiving the information about the project; ***Questionnaire 2 (Q2)***- 2 weeks after receiving test results

Knowledge was assessed (Q1 and Q2) through 15 true/false questions about concepts covered during the pre-test information session or online module. Anxiety scores were measured (Q1 and Q2) using the 6-item Spielberger State-Trait Anxiety Inventory (STAI-6). Scores range from 6-24, with 6 indicating no anxiety and 24 very high anxiety[36]. Participants were also asked about their perceived risks of developing cancer (Q1 and Q2).

Decisional conflict scale (DCS) scores[37] were measured (Q1) for total decisional conflict and the "uncertainty", "uninformed", "values clarity" and "support" subscales. The possible range is 0 (no conflict) – 100 (extreme conflict). Decisional regret was measured using a validated 5-item scale [range 0-100][38] (Q2), and test-related distress and positive experiences were measured using a 10-item validated scale[39] (Q2). Test-related distress had a range 0-30 and positive experiences were reverse-scored, with a possible range from 0 (completely positive experiences) to 20 (no positive experiences). Overall satisfaction with the testing process was measured using a 5-point Likert scale (Q2).

Participants were also asked about their perceived risks of developing cancer at Q1 and Q2. This was assessed using both a 5-point Likert scale comparing their own risk to the general population, as well as a scale of 1 (no chance) to 100 (definitely).

Sydney – online tool

Sydney participants accessed pre-test information and provided consent through an interactive online tool, after which a buccal swab kit was posted to them with a reply-paid envelope.

Melbourne – community sessions

Melbourne JeneScreen participants received information by attending an in-person group session. At "primed sessions", attendees (generally ~100) registered for the purpose of JeneScreen participation. "Unprimed" attendees attended a Jewish community event for an unrelated reason, such as a public lecture, and were offered JeneScreen testing.

A genetic counsellor facilitated each session (primed/unprimed) and covered the same material as the Sydney online tool. Attendees could provide consent and provide a DNA sample at the event, or take a buccal swab kit home along with a reply-paid envelope.

The procedure for returning results to Sydney and Melbourne participants with and without B-JFM is published in the methodology paper[35].

Data analysis

Results are reported for each cohort - Melbourne (M) and Sydney (S) - and as a combined cohort (M+S). All data were analysed using IBM SPSS Statistics v26. An initial correlation matrix for all outcome scales was created to check for outliers. All data were normally distributed. Parallel analyses were used to determine the number of components to retain for each continuous scale in an exploratory factor analysis of all scales. Principal component analysis with oblimin rotation was used to examine item loadings and to explore the dimensionality and internal consistency of the scales. No items were excluded as a result. Cronbach's alpha of all scales was above 0.75 showing high internal consistency.

Descriptive statistical analyses were carried out to detect statistically significant differences between the Sydney and Melbourne cohorts, as well as between individuals with and without a B-JFM, and high- and low-risk individuals. Continuous unpaired variables were compared using independent samples t-tests (two categories) and one-way analysis of variance (ANOVA) (>two categories). Paired continuous data were compared using paired sample t-tests. Paired and unpaired categorical data were compared using McNemar and Pearson's Chi square tests, respectively.

Multiple linear regression models were used for continuous outcome variables. Logistic regression was used for recoded binary outcome variables (risk perception). All regression models were adjusted for age, sex, education levels, number of children, number of grandparents, Sephardic Jewish background, and healthcare worker (HCW) status (self-reported medical/allied health training). For linear and logistic regression models, residuals were checked for normality and Lemeshow and Homer's goodness-of-fit tests were conducted, respectively. Variance inflation factor (VIF) to assess collinearity, standardised residuals to detect and evaluate outliers and Cook's distance to identify influential cases were used in linear regression models. Due to multiple testing, a threshold significance level of 0.01 and a confidence interval of 99% were used.

RESULTS

Demographics

Summary demographics are set out in Table 1. Compared to Sydney, the Melbourne cohort was older, had a higher proportion of male participants, fewer participants with at least University education, a larger range in family size (but the same median number of children), and a greater proportion with all four grandparents being Jewish.

Table 1– Demographic characteristics of the JeneScreen study population

	Total	**Sydney**	**Melbourne**	**P value (Syd vs Mel)**
Mean age in years (+/_ SD)	n=2274 48 (14)	n=624 45 (13)	n=1650 49(14)	<0.001
	n (%)	n (%)	n (%)	
Sex Male Female	n=2272 575 (25.3) 1697 (74.7)	n=625 120 (19.2) 505 (80.8)	n=1647 455 (27.6) 1192 (72.4)	<0.001
Relationship status Separated/Divorced/Widowed Single (never married) Married or de facto	n=2263 173 (7) 213 (9.4) 1877 (82.9)	n=622 36 (5.8) 67 (10.8) 519 (83.4)	n=1641 137 (8.3) 146 (8.9) 1358 (82.8)	0.061
Highest level of education Year 10 or below/other Year 12/TAFE certificate/diploma University undergraduate/ Higher degree	n=2264 50 (2.2) 430 (19.0) 1784 (78.8)	n=624 3 (0.5) 104 (16.7) 517 (82.9)	n=1640 47 (2.9) 326 (19.9) 1267 (77.3)	<0.001
Medical/allied health training Yes No	n=2262 555 (24.5) 1707 (75.5)	n= 622 146 (23.5) 476 (76.5)	n= 1640 409 (24.9) 1231 (75.1)	0.235
Current employment situation Unemployed/Student/Home duties/Retired or on pension/other Full time/Part time/Self-employed	n= 2244 512 (22.8) 1732 (76.0)	n= 618 134 (21.7) 484 (78.3)	n= 1626 378 (23.2) 1248 (76.8)	0.430
Number of children 0 1-3 ≥4	n= 2254 351 (15.6) 1675 (74.3) 228 (10.1)	n= 620 116 (18.7) 435 (70.2) 69 (11.0)	n= 1634 235 (14.4) 1240 (75.9) 159 (9.7)	0.016
Median number of children (range) **Mean (SD)**	2 (0-13) 2.1 (1.3)	2 (0-8) 1.9 (1.3)	2 (0-13) 2.3 (1.4)	<0.001
Ashkenazi Jewish Yes No	n= 2249 2125 (94.5) 124 (5.5)	n= 626 592 (94.6) 34 (5.4)	n= 1623 1533 (94.5) 90 (5.5)	0.915
Sephardic Jewish Yes No	n= 2183 170 (7.8) 2013 (92.2)	n= 617 62 (10.0) 555 (90)	n= 1566 108 (6.9) 1458 (93.1)	0.014
Number of Jewish grandparents <4 4	n=1872 215 (11.5) 1657 (88.5)	n= 623 90(14.8) 520 (85.2)	n= 1262 125(9.9) 1137 (90.1)	0.002

TAFE = Technical and Further Education (vocational training)

Recruitment and testing outcomes

The overall B-JFM detection rate of tested participants was 1.3% (n= 28/2167). There were 11 males and 17 females with a B-JFM. There was no statistically significant difference (χ^2=2.014, p=0.156) between detection rates in Sydney (0.8%) and Melbourne (1.5%). Family history-based risk could be

calculated for 2144 participants, of whom 93% (n=1999) fell within the low-risk category (Manchester score <12) and 7% (n=145) fell within the high-risk category (Manchester score ≥12).

Only two of the 28 participants with a B-JFM (7.1%) had a significant family history of breast/ovarian/prostate/pancreatic cancer (Manchester score ≥12), and none had a personal cancer history. Seventeen participants with a B-JFM (60.7%) had some family history of relevant cancers but a Manchester score <12. The remaining nine participants (32.1%) reported no relevant cancer history and would not have been eligible for this testing in a clinical setting. Figures 1 and 2 show recruitment and testing outcomes for the Sydney and Melbourne cohorts.

Sydney

Of 750 community members who registered online, 84% (n=630/750) completed the online module (see Fig 1). Of those, 97.0% (n=611/630) consented to testing and 97.3% (n=594/611) returned a sample. Five participants (0.8%) had a B-JFM, from five different families.

Melbourne

Of 1775 community members who attended a group session, 93.0% (n=1650/1775) agreed to participate and 1573 consented to testing (see Fig 2). Overall, 23 Melbourne participants (1.5%) had a B-JFM, two of whom were first-degree relatives of another participant with a B-JFM, leaving 21 different families (1.3%). These proportions (1.5% and 1.3%) are not significantly different (2-tailed z-test, $p>0.05$); thus we have reported the full number of participants with a B-JFM (n=23).

Across 20 community sessions, the average testing uptake at events was 83.3% (n=1478/1775). Of 169 participants who took swabs home, 95 returned them (56.2%). The total average uptake (including returned swabs) was 88.6% (n=1573/1775). The average uptake was 50.0% (n=63/126) for the three unprimed sessions and 91.6% (n=1510/1649) for the 17 primed sessions.

Table 2 shows a summary of mean psychological outcomes for Sydney and Melbourne participants.

Mean psychological outcomes by high and low risk (Table S1); educational status (Table S2) and HCW (Table S3) status are included in the Supplementary Materials.

Table 2: Mean psychological outcomes for Sydney and Melbourne participants

				Unadjusted model		Adjusted Model	
	Total	**Sydney Mean (SD)**	**Melbourne Mean (SD)**	**Beta**	**p value**	**Beta**	**p value**
Knowledge score Q1	11.7 (2.9)	10.7 (2.8)	12.1 (2.9)	0.231	<0.001	0.269	<0.001
Knowledge Score Q2	11.6 (2.4)	11.2 (2.4)	11.7 (2.4)	0.100	<0.001	0.141	<0.001
STAI score Q1	9.9 (3.5)	9.7 (3.2)	10.0 (3.7)	0.207	0.240	0.368	0.035
STAI score Q2	9.6 (3.3)	9.7 (3.3)	9.5 (3.3)	-0.264	0.145	-0.133	0.458
DCS	5.8 (11.9)	6.7 (12.8)	5.4 (11.3)	-1.575	0.008	-1.933	0.003
DCS uncertainty	5.2 (16.0)	4.9 (16.4)	5.3 (15.7)	0.333	0.673	-0.012	0.988
DCS uninformed	7.1 (16.0)	9.5 (18.1)	5.8 (14.8)	-4.020	<0.001	-4.307	<0.001
DCS values clarity	9.3 (20.8)	10.6 (22)	8.7 (20.2)	-2.295	0.029	-2.768	0.001
DCS Support	2.7 (9.2)	2.6 (9.5)	2.8 (9.1)	0.056	0.905	-0.120	0.874
DRS	7.3 (13.0)	7.2 (13.7)	7.4 (12.7)	-0.020	0.978	0.019	0.979
Distress	0.8 (2.2)	0.8 (2.0)	0.8 (2.3)	-0.055	0.650	-0.066	0.584
Positive Experiences	3.4 (4.5)	3.4 (4.6)	3.4 (4.4)	-0.017	0.943	-0.168	0.549

DCS = decisional conflict scale; DRS = decisional regret scale
The models were adjusted for age, sex, education levels, healthcare worker (HCW) status, number of children, number of grandparents and Sephardic Jewish background.

T**able 3: Knowledge and STAI at Q1 and Q2 for the combined cohort (M+S)**

			Unadjusted model		Adjusted Model	
	Q1 Mean (SD)	**Q2 Mean (SD)**	**Beta**	**p value**	**Beta**	**p value**
Knowledge score	11.7 (2.9)	11.6 (2.4)	-0.023	0.170	-0.022	0.180
STAI score	9.9 (3.5)	9.6 (3.3)	-0.040	0.018	-0.038	0.024

The models were adjusted for age, sex, education levels, HCW status, number of children, number of grandparents and Sephardic Jewish background. Q1 scores were not used as a covariate in the models as there was a weak correlation between scores of Q1 with Q2.

Knowledge

The Melbourne and Sydney mean knowledge score at Q1 was 11.7 (+/-2.9) out of 15 (Table 3). This was not significantly different from the mean score at Q2 of 11.6 (+/- 2.4)β=-0.2, p=0.180). Both the Melbourne Q1 (12.1+/-2.9) and Q2 (11.7+/-2.4) mean scores were significantly higher than Sydney scores (Q1: 10.7+/-2.8, β=0.3, p<0.001; Q2: 11.2+/-2.4, β=0.1, p<0.001) (Table 2).

There were no significant differences between mean knowledge scores of high-risk and low-risk (p=0.646), or B-JFM-negative and B-JFM-positive (β=-0.2, p=0.587) participants. The mean scores were significantly lower for participants with ≤Year 10 (9.8+/-3.5) compared with those with Year 12/TAFE (10.7+/- 3.1, p=0.038) and those with a higher degree (11.9+/-2.5, p<0.001). HCW had significantly higher scores (12.4+/-2.1) than non-HCW (11.3+/-2.8, p<0.001).

Decisional conflict

The mean total decisional conflict scale (DCS) score overall was 5.8 (+/-11.9,[0-100]). The mean Melbourne DCS score (5.4+/- 11.3) was significantly lower than the mean Sydney score (6.7+/-12.8, β=-1.9, p=0.003), with a low level of conflict in both cohorts. The mean Melbourne scores were also significantly lower for the “uninformed” (p<0.001) and “values clarity” (p=0.001) subscales. There were no significant differences for DCS scores or sub-scores between those with a B-JFM and those without a B-JFM (p=0.419) or high-risk and low-risk participants (p=0.838).

Participants with a higher level of education had significantly lower mean DCS scores (5.3+/-11.6) than those with ≤year 10 (10.9+/-15.5, p=0.008) and year 12/TAFE (7.5+/-12.1, p=0.012). HCW had significantly lower DCS scores (4.5+/-9.8) compared with non-HCW (6.3+/-12.4, p=0.002). The “uninformed” and “values clarity” sub-scores showed the same trend for education level and HCW status.

Anxiety and test-related distress/positive experiences

The Melbourne and Sydney mean Q1 STAI-6 score was 9.9 (+/-3.5; range [6-24]) and did not decrease significantly at Q2 (9.6+/-3.3, β=-0.04, p=0.024). Mean scores for Sydney and Melbourne participants did not differ significantly between sites from Q1 to Q2 (β=0.4, p=0.035 and β=-0.1, p=0.458 respectively), but Melbourne scores decreased significantly at Q2 (p=0.001), while Sydney scores did not (p=0.913). There were no significant differences between low-risk and high-risk participants' STAI scores at Q1 (β=0.7, p=0.030) or Q2(β=0.5, p=0.135). Q1 scores were not significantly different between those with a B-JFM- and those without a B-JFM (β=0.03, p=0.968). Q2 scores in those with a B-JFM (12.4+/-5.1) were not significantly different than their Q1 scores (9.7+/-2.6, p=0.037). However, Q2 scores were higher in those with a B-JFM (12.4+/-5.1) than those without a B-JFM (9.6+/-3.3, β=2.9, p<0.001).

The overall mean test-related distress score was 0.8 (+/-2.2,[0-30]), with no significant differences between scores for Sydney and Melbourne participants (β=-0.07, p=0.584) or low-risk and high-risk participant scores (p=0.110). The mean score for those with a B-JFM-was significantly higher (10.9+/-8.2) than for those without a B-JFM (0.7+/-1.7, β=10.3, p<0.001).

The M+S mean (reverse-scored) positive experience score was 3.4 (+/-4.5,[1-20]), with no significant difference between Sydney and Melbourne scores (β=-.17, p=0.549). Mean scores were significantly higher (less positive experience) for those with a B-JFM (7.8+/-3.5) than those without a B-JFM (3.4+/-4.4, β=4.2, p<0.001).

Decisional regret

The M+S mean decisional regret score was 7.4(+/-13.0,[0-100]) with no significant difference between Sydney and Melbourne (β=0.02, p=0.979), individuals with and without a B-JFM (p=0.500), or low-risk and high-risk participants (β=-1.5, p=0.245).

Risk perception

Table S4 (Supplementary Materials) shows logistic regression models for participants' perceived risks of having a B-JFM and developing ovarian cancer, breast cancer (women only) and prostate cancer (men only) (for percentage figures, see Table 4). For Q1, a significantly higher percentage of Melbourne (48.5%) than Sydney (37.9%) participants perceived their risk of having a B-JFM as high/very high (p=0.001). Similarly, a significantly higher percentage of Melbourne participants perceived their breast (44.7%) and ovarian (34.3%) cancer risks to be high/very high, than Sydney participants (29.0% and 21.6% respectively, p<0.001). This trend was maintained at Q2 for breast and ovarian cancer risks.

For Q1, there were no significant differences in risk perception between individuals assessed (based on reported family history) as being low- and high-risk for self-perceived risks of having a B-JFM or developing cancer. For Q2, however, a significantly higher percentage of high-risk participants perceived their breast (36.8%) and ovarian (20.0%) cancer risk to be high/very high than low-risk participants (12.3% and 7.6% respectively, p≤0.001). No differences in risk perception were seen for prostate cancer for Q1 or Q2.

Prior to receiving results, 38.6% of low-risk women classified themselves as being at high risk of breast cancer and 29.4% as being at high risk of ovarian cancer. However, after receiving results, the number of low-risk women who perceived their risk as high, decreased significantly (12.3% [breast cancer], 7.6% [ovarian cancer];p<0.001). The proportion of high-risk women who perceived their risk as high did not change significantly. A significant decrease was observed for men at low-risk for prostate cancer (39.0% vs 12.6%;p<0.001) after results, with no significant change for high-risk men (36.4% vs 22.7%;p=0.030).

Table 4: Assessment of risk based on family history

Assessment of risk based on family history	**Low risk**					**High risk**				
	Total	**Risk perception n (%)**				**Total**	**Risk perception n (%)**			
		Low	**Medium**	**High**	**p values of comparison of high-risk perception over time**		**Low**	**Medium**	**High**	**p values of comparison of high-risk perception over time**
Chance of a *BRCA1* or *BRCA2* PV compared to an average person of the same age (Q1 only)										
Q1	1706 (92.9)	303 (17.8)	643 (37.7)	760 (44.5)		129 (7.1)	17 (13.2)	47 (36.4)	65 (50.4)	
Chances of developing BREAST cancer in future compared to an average woman of the same age										
Q1	1262 (92.3)	163 (12.9)	612 (48.5)	487 (38.6)	<0.001	105 (7.7)	8 (7.6)	46 (43.8)	51 (48.6)	0.018
Q2	1181 (92.6)	209 (17.7)	827 (70.0)	145 (12.3)		95 (7.4)	8 (8.4)	52 (54.7)	35 (36.8)	
Chances of developing OVARIAN cancer in future compared to an average woman of the same age										
Q1	1251 (92.3)	168 (13.4)	715 (57.2)	368 (29.4)	<0.001	105 (7.7)	14 (13.3)	53 (50.5)	38 (36.2)	0.010
Q2	1180 (92.5)	226 (19.2)	864 (73.2)	90 (7.6)		95 (7.5)	15 (15.8)	61 (64.2)	19 (20.0)	
Chances of developing PROSTATE cancer in future compared to an average man of the same age										
Q1	403 (94.8)	57 (14.1)	189 (46.9)	157 (39.0)	<0.001	22 (5.2)	4 (18.2)	10 (45.5)	8 (36.4)	0.030
Q2	357 (94.2)	63 (17.6)	249 (69.7)	45 (12.6)		22 (5.8)	1 (4.5)	16 (72.7)	5 (22.7)	

Satisfaction

Overall, 93.2% of participants were satisfied/very satisfied with the JeneScreen program, with no significant differences between Sydney (92.3%) and Melbourne (93.6%) (χ^2=1.044, p=0.593). There was no significant difference between those with and without a B-JFM ((χ^2=0.310, p=0.856).

DISCUSSION

This study has evaluated and compared two different population-level B-JFM testing programs, one an online program and the other a face-to-face group education and screening program. No major differences were found between the two in terms of anxiety, knowledge, satisfaction and decisional regret.

At present, the Australian national health system, Medicare, only funds genetic testing for individuals with a diagnosis of breast or ovarian cancer and where there is at least a 10% chance of identifying a mutation. Genetic testing may be funded by individual public Family Cancer Clinics, but criteria vary. Most Family Cancer Clinics will provide B-JFM testing to anyone of Jewish ancestry with a personal or family history of breast cancer diagnosed before age 50 or epithelial ovarian cancer at any age. Of 28 individuals identified with a B-JFM in this study, over 30% did not have any relevant personal or family cancer history and would have remained unaware of their risk status without the testing provided by this study. This reinforces the importance of population-level screening to identify at-risk individuals who would not qualify for testing through current Australian Medicare or most institutional guidelines, and adds to the body of evidence from various Jewish communities and across differing health care systems supporting Jewish population screening and not only personal/family history-based testing.

The overall detection rate of 1.30% is lower than reported in some studies[13 40] but similar to that in a Canadian population-screening program[12]. We expected a reduced detection rate, given the eligibility criteria excluded individuals with previous *BRCA1/2* testing, a blood relative with a *BRCA1/2* PV, or a recent cancer diagnosis in the preceding 12 months. These criteria were intended to maximize the study's impact by identifying previously undetected at-risk families. Thus, much of the "low-hanging fruit" – families with significant cancer history– - was excluded from our study.

Minimising harmful psychological impacts associated with genetic testing is one of the key factors that must be considered in developing genetic testing programs[41]. Our findings demonstrate that, regardless of recruitment strategies, anxiety levels (STAI scores) reported in both population-level testing programs were low, similar to anxiety levels reported in other studies assessing *BRCA1/2* testing in clinical practice[33 42], as well as other B-JFM population screening programs[13 23].

Consistent with other studies[23 43], participants with a B-JFM had higher post-result anxiety and test-related distress and lower positive experiences, than those without a B-JFM. However, the mean STAI score for those with a B-JFM was within the range reported in a study where *BRCA1/2* results were notified clinically[42], as well as a UK study comparing B-JFM population screening with criteria-based testing[13]. Based on previous studies, it is expected that anxiety and distress in those with a B-JFM will reduce to pre-testing levels within 6-12 months from result disclosure[16 44 45]. As part of the ongoing JeneScreen data collection, participants with a B-JFM receive 12- and 24-month questionnaires; this data will be analysed and published separately. Importantly, decisional regret was not different for participants with and without a B-JFM, indicating that on average, neither group regretted their decision to be tested.

This study has demonstrated the impact of participation in a B-JFM testing program on cancer risk perception of individuals whose self-reported cancer history indicated low risk. Our findings suggest that untested Jewish individuals, who are aware of the prevalence of B-JFM, may perceive themselves at high risk of related cancers, irrespective of their cancer family history. A Canadian Jewish population-based B-JFM program found that one year after testing, the average breast cancer risk estimate reduced only slightly from 35.8% to 33.5% (p=0.08)[23]. This was despite each participant receiving a personalised risk assessment (average risk 11.4%). In contrast, JeneScreen has significantly improved the accuracy of cancer risk perception for both men and women at low risk without affecting the risk perception of those at high risk.

The program was highly acceptable, with very high satisfaction rates across the cohorts, consistent with findings of other B-JFM programs[13 23 40]. The uptake for the program was very high in both Melbourne and Sydney, and the Melbourne program was able to demonstrate high interest even amongst individuals who had attended an independent event without the specific purpose of having

testing. The higher numbers recruited in the Melbourne program may provide support for the methodology of using community ambassadors and trusted institutions to raise awareness and attract participation in community-based studies. A recent survey of Australian Jewry found that "Jews in Melbourne generally exhibit a more intensive level of Jewish identity than Jews in Sydney", which may have contributed to the higher uptake through communal gatherings in Melbourne rather than the individualised online program in Sydney[46]. Alternatively, the lower numbers tested in Sydney could have been due to fewer knowing about the program than was the case for those in Melbourne. Future research could explore this by offering each program at the alternate site.

The mean knowledge scores in Melbourne were slightly but significantly higher pre-test and post-result than Sydney. This suggests that some elements of the Melbourne program, where information was delivered in a face-to-face presentation with an opportunity to ask questions in the group or personally at the event, increased the levels of understanding and retention of information somewhat above the provision of information online. This is supported by the finding of slightly higher "uninformed" DC scores in Sydney compared with Melbourne, suggesting that Sydney participants in the online screening program both retained slightly less knowledge and felt less informed throughout the process.

Nevertheless, mean knowledge scores were high across both cohorts, demonstrating that both educational methodologies ultimately led to reasonably good knowledge, and that participants in both programs retained adequate information to make an informed decision about whether or not to have testing. International programs have found participant satisfaction and information retention across various methods of information provision, consent and counselling, demonstrating broad acceptability of varied methodologies[13 14 23 25 31-33]. The online JeneScreen program has integrated well with the increase of telehealth and digital health options through the COVID-19 pandemic. Despite some advantages of the community-based program, both Sydney and Melbourne

Jewish communities are considering implementing ongoing online programs to provide B-JFM testing.

Strengths of our study include a large number of participants (>2000) across two large Australian Jewish populations. The study provides a robust evaluation of two interventions with differing methodology. The American College of Medical Genetics and Genomics (ACMG) recently published up-to-date guidelines regarding DNA-based screening[47]. These guidelines, together with the accompanying commentary[48] highlight the importance of integrating population DNA-based screening programs within established, evidence-based clinical care for risk reduction. In accordance with the ACMG guidance, the care of B-JFM positive JeneScreen participants and their families has been integrated into the (publicly funded) Australian medical system.

Limitations of the study include the potential for self-selection bias. Because the study was designed as a population-based offering, with minimal inclusion/exclusion criteria, selection by the researchers did not take place. It is possible that participants were more likely to rate the program positively than an unselected group of Jewish individuals. Further, only participants from Sydney and Melbourne were eligible to participate. Although these cities were chosen as they have the largest Jewish populations in Australia, this may limit the generalisability to Jewish populations in other Australian cities. Each protocol was only offered in one city. Although the findings were adjusted for confounders, we cannot exclude the possibility that the differences between each protocol reflect an intrinsic difference between the cohorts in Sydney and Melbourne that was not captured in the variables that we measured. In any event, both programs were successful, irrespective of recruitment methodology. Due to the small numbers of participants with a B-JFM, the comparisons have limited generalisability. However, further clinically significant outcomes amongst individuals with and without B-JFM may arise in future studies.

CONCLUSION

Our study evaluated and compared two different B-JFM screening programs in two Australian Jewish communities. Both programs were highly acceptable to the tested cohorts, with high rates of satisfaction and low scores in anxiety, decisional conflict/regret and distress. Out of 28 individuals with B-JFM, more than 30% would not have qualified for *BRCA1/2* testing under current Australian guidelines, reinforcing the importance of population-level screening to identify at-risk individuals in the community.

Author contributions

JT, NC, BM, KBS, RK, AB, LB, CJ, PJ, AT, SN, LA and MD were involved in conception and/or design of the study. NC and JT are also responsible for implementing the protocol, data acquisition and manuscript drafting. MD and LA are also responsible for critical revision of the work. RK is responsible for data analysis. IC, SM, SR and YK were involved with laboratory protocol development and data acquisition. All authors reviewed drafts of the manuscript.

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Competing interests statement

The authors declare no competing interests.

Ethics approval

Institutional Human Research Ethics Committee approval was obtained from the South Eastern Area Health Service Human Research Ethics Committee: HREC Ref 16/125. Governance approval was obtained from the Royal Children's Hospital Human Research Ethics Committee: HREC Ref 37314A.

Figure legends

Figure 1: Recruitment and testing outcomes for the Sydney cohort

Figure 2: Recruitment and testing outcomes for the Melbourne cohort

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Table S1: Mean psychological outcomes by low and high risk

	Total	**Low Risk** **Mean (SD)**	**High Risk** **Mean (SD)**
Knowledge score Q1	11.7 (2.9)	11.7 (3.0)	11.6 (2.9)
Knowledge **Score Q2**	11.6 (2.4)	11.5 (2.4)	11.8 (2.0)
STAI score Q1	9.9 (3.5)	9.8 (3.5)	10.5 (3.9)
STAI score Q2	9.6 (3.3)	9.6 (3.3)	10.0 (3.4)
DCS	5.8 (11.9)	5.8 (12.0)	5.6 (9.7)
DCS uncertainty	5.2 (16.0)	5.4 (16.2)	3.2 (11.8)
DCS uninformed	7.1 (16.0)	7.0 (16.0)	7.3 (14.4)
DCS values clarity	9.3 (20.8)	10.6 (22)	8.7 (20.2)
DCS Support	2.7 (9.2)	2.7 (9.4)	2.2 (8.0)
DRS	7.3 (13.0)	7.5 (13.2)	6.1 (12.0)
Distress	0.8 (2.2)	0.8 (2.2)	1.1 (2.1)
Positive Experiences	3.4 (4.5)	3.4 (4.5)	3.2 (4.6)

Table S2: Mean psychological outcomes by education status

	Total	**Year 10 below/other Mean (SD)**	**Year 12/Tafe Mean (SD)**	**Higher degree Mean (SD)**
Knowledge score Q1	11.7 (2.9)	9.6 (4.4)	10.7 (3.5)	12.0 (2.7)
Knowledge Score Q2	11.6 (2.4)	10.2 (2.4)	10.7 (2.6)	11.8 (2.3)
STAI score Q1	9.9 (3.5)	9.6 (3.6)	9.8 (3.5)	9.9 (3.5)
STAI score Q2	9.6 (3.3)	9.6 (3.7)	9.6 (3.5)	9.6 (3.3)
DCS	5.8 (11.9)	10.9 (15.5)	7.5 (12.1)	5.3 (11.6)
DCS uncertainty	5.2 (16.0)	5.4 (16.2)	3.2 (11.8)	3.2 (11.8)
DCS uninformed	7.1 (16.0)	13.6 (21.5)	9.8 (16.7)	6.3 (15.6)
DCS values clarity	9.3 (20.8)	16.4 (27.4)	11.8 (20.7)	8.6 (20.6)
DCS Support	2.7 (9.2)	5.3 (12.3)	2.8 (9.3)	2.6 (9.1)
DRS	7.3 (13.0)	7.5 (13.2)	6.1 (12.0)	6.1 (12.0)
Distress	0.8 (2.2)	0.9 (1.8)	0.9 (2.7)	0.8 (2.1)
Positive Experiences	3.4 (4.5)	4.6 (6.5)	3.5 (4.7)	3.4 (4.3)

Table S3: Mean psychological outcomes by health care worker status

	Total	**Not HCW Mean (SD)**	**HCW Mean (SD)**
Knowledge score QS4	11.7 (2.9)	11.4 (3.1)	12.5 (2.2)
Knowledge Score Q2	11.6 (2.4)	11.3 (2.4)	12.4 (2.0)
STAI score Q1	9.9 (3.5)	9.8 (3.5)	9.9 (3.5)
STAI score Q2	9.6 (3.3)	9.7 (3.4)	9.4 (3.1)
DCS	5.8 (11.9)	6.3 (12.4)	4.5 (9.8)
DCS uncertainty	5.2 (16.0)	5.5 (16.3)	4.2 (14.1)
DCS uninformed	7.1 (16.0)	7.8 (16.9)	4.7 (12.8)
DCS values clarity	9.3 (20.8)	10.0 (21.5)	7.3 (18.2)
DCS Support	2.7 (9.2)	2.7 (9.4)	2.6 (8.9)
DRS	7.3 (13.0)	7.5 (13.4)	6.9 (12.0)
Distress	0.8 (2.2)	0.8 (2.3)	0.7 (2.0)
Positive Experiences	3.4 (4.5)	3.4 (4.5)	3.5 (4.4)

Table S4 Logistic regression models comparing perceived risk of having a *BRCA1/2* pathogenic variant, breast cancer, ovarian cancer and prostate cancer by location and risk level

	OR (95% CI)	p value	aOR (95% CI)	p value
Chance of a *BRCA1* or *BRCA2* PV compared to an average person of the same age (Q1 only)				
Location				
Sydney	Ref	**0.001**	---------	--------
Melbourne	1.6 (1.2-2.2)			
Risk				
Low	Ref	0.128	---------	--------
High	1.5 (0.9-2.7)			
Chances of developing BREAST cancer in future compared to an average woman of the same age				
Location				
Sydney	Ref	**<0.001**	Ref	**<0.001**
Melbourne	2.3 (1.1-5.1)		2.6 (1.6-4.2)	
Risk				
Low	Ref	0.039	Ref	**<0.001**
High	2.3(1.6-3.4)		7.2 (3.1-17.2))	
Chances of developing OVARIAN cancer in future compared to an average woman of the same age				
Location				
Sydney	Ref	**<0.001**	Ref	**0.001**
Melbourne	2.3 (1.5-3.5)		2.7 (1.5-4.8)	
Risk				
Low	Ref	0.304	Ref	**0.001**
High	1.4 (0.7-2.9)		3.9 (1.8-8.6)	
Chances of developing PROSTATE cancer in future compared to an average man of the same age				
Location				
Sydney	Ref	0.451	0.9 (0.4-2.4)	0.964
Melbourne	1.3 (0.6-2.7)			
Risk				
Low	Ref	0.757	Ref	0.083
High	0.8 (0.2-2.9)		6.9 (0.8-63.1)	

*aOR: Adjusted ORs. CI: Confidence Intervals

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2022-02-17 Figure 2.jpg