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Randomised trial of population-based *BRCA* testing in Ashkenazi Jews: long-term outcomes

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Objective Unselected population-based *BRCA* testing provides the opportunity to apply genomics on a population-scale to maximise primary prevention for breast-and-ovarian cancer. We compare long-term outcomes of population-based and family-history (FH)/clinical-criteria-based *BRCA* testing on psychological health and quality of life.

Design Randomised controlled trial (RCT) (ISRCTN73338115) GCaPPS, with two-arms: (i) population-screening (PS); (ii) FH/clinical-criteria-based testing.

Setting North London Ashkenazi-Jewish (AJ) population.

Population/Sample AJ women/men.

Methods Population-based RCT (1:1). Participants were recruited through self-referral, following pre-test genetic counselling from the North London AJ population.*Inclusion criteria*: AJ women/men >18 years old; exclusion-criteria: prior *BRCA* testing or first-degree relatives of *BRCA*-carriers.*Interventions*: Genetic testing for three Jewish *BRCA* founder-mutations: 185delAG (c.68_69delAG), 5382insC (c.5266dupC) and 6174delT (c.5946delT), for (i) all participants in PS arm; (ii) those fulfilling FH/clinical criteria in FH arm. Linear mixed models and appropriate contrast tests were used to analyse the impact of *BRCA* testing on psychological and quality-of-life outcomes over 3 years.

Main outcome measures Validated questionnaires (HADS/MICRA/HAI/SF12) used to analyse psychological wellbeing/quality-of-life outcomes at baseline/1-year/2-year/3-year follow up.

Results In all, 1034 individuals (691 women, 343 men) were randomised to PS (n = 530) or FH (n = 504) arms. There was a statistically significant decrease in anxiety (P = 0.046) and total anxiety-&-depression scores (P = 0.0.012) in the PS arm compared with the FH arm over 3 years. No significant difference was observed between the FH and PS arms for depression, health-anxiety, distress, uncertainty, quality-of-life or experience scores associated with *BRCA* testing. Contrast tests showed a decrease in anxiety (P = 0.018), health-anxiety (P < 0.0005) and quality-of-life (P = 0.004) scores in both PS and FH groups over time. Eighteen of 30 (60%) *BRCA* carriers identified did not fulfil clinical criteria for *BRCA* testing. Total *BRCA* prevalence was 2.9% (95% CI 1.97–4.12%), *BRCA1* prevalence was 1.55% (95% CI 0.89–2.5%) and *BRCA2* prevalence was 1.35% (95% CI 0.74–2.26%).

Conclusion Population-based AJ *BRCA* testing does not adversely affect long-term psychological wellbeing or quality-of-life, decreases anxiety and could identify up to 150% additional *BRCA* carriers.

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Trial registry: ISRCTN-73338115.

Keywords Ashkenazi Jews, *BRCA1*, *BRCA2*, genetic testing, population testing, psychological, quality-of-life.

Tweetable abstract Population *BRCA* testing in Ashkenazi Jews reduces anxiety and does not adversely affect psychological health or quality of life.

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Introduction

Traditionally, ovarian cancer (OC) and breast cancer (BC) prevention has been targeted at high-risk individuals like *BRCA1/BRCA2* carriers. Such *BRCA1/BRCA2* carriers have a 17–44% OC risk and 69–72% BC risk up to age 80 years.[1] Carrier identification offers the opportunity of screening/prevention to reduce the burden of BC/OC in women. At-risk *BRCA*-mutation carriers have a range of options to minimise risk: risk-reducing salpingo-oophorectomy to reduce their OC risk;[2,3] magnetic resonance imaging/mammography screening, risk-reducing mastectomy,[4], or chemoprevention with selective estrogen-receptor modulators to reduce their BC-risk;[5] as well as preimplantation genetic diagnosis.[6] The current practice of clinical-criteria/family-history (FH) -based *BRCA* testing is only moderately effective at identifying mutations and has poor ability to rule out their absence.[7] Inadequate public and health-professional awareness, complexity of the current structure/referral pathways and limited genetic-counselling services have led to restricted access and under-utilisation of genetic-testing services.[8–10] Population testing overcomes the limitations of the current FH/criteria-based testing, enabling the identification of many more at-risk *BRCA* carriers.

Population-based *BRCA* testing has been investigated in the Ashkenazi-Jewish (AJ) population. It was found to be feasible, acceptable,[11] cost-effective, with high satisfaction, and deliverable in a community setting using non-inferior, cost-efficient pre-test counselling approaches.[12–15] Israeli and Canadian population-cohort studies show increased anxiety/distress in mutation carriers at 6 months/1 year.[16,17] These studies provided only post-test counselling. However, overall satisfaction rates were high and similar for carriers and non-carriers (>91%).[16,17] Short-term increase along with long-term decrease in distress and uncertainty have also been reported following *BRCA* testing in high-risk women.[16,18–21] Some studies also found increase and no change in anxiety or depression over 1 year in high-risk women.[20] The Genetic-Cancer-Prediction through Population-Screening (GCaPPS) study is the only randomised controlled trial (RCT) directly comparing *BRCA* testing using FH-based clinical criteria with population screening (PS) or *BRCA* testing of all participants irrespective of FH (ISRCTN: 73338115). Short-term (3-month) outcomes demonstrated that population testing (compared with FH testing) did not adversely affect psychological wellbeing or quality of life, while overall anxiety and uncertainty decreased at 3 months of follow up.[14] However, psychosocial outcomes of *BRCA* testing may change with time and long-term consequences can differ from short-term outcomes. RCT data of long-term psychological-health and quality-of-life outcomes of population-based *BRCA* testing have not previously been reported. In this paper we report on 3-year psychosocial/quality-of-life outcomes from the GCaPPS trial.

Methods

Design

An RCT (ISRCTN73338115) with participants randomly allocated to one of two arms: PS arm and FH arm. Inclusion criteria were age >18 years and AJ ethnicity. Exclusion criteria were known *BRCA* mutation, first-degree-relative of a *BRCA* carrier or previous *BRCA* testing. Recruitment was undertaken via self-referral through the North-London Jewish community. Study leaflets were made available through community charities, religious groups, a local pharmacy chain (Boots) and the study website. All participants received structured nondirective pre-test genetic counselling before consenting for *BRCA* testing. Baseline data were collected at the initial appointment. Consenting participants were randomised (1:1) post-counselling using a computer-generated random-number algorithm. Genetic counsellors were blinded to group allotment during counselling and recruitment. Participants were notified of their allocated group by post. Randomisation was undertaken 3 weeks after consent to provide a window period for early withdrawal before genetic testing in case volunteers changed their mind. These details have been described earlier.[14]

BRCA testing for the three AJ founder mutations [185delAG (c.68_69delAG), 5382insC (c.5266dupC) and 6174delT (c.5946delT)] was performed in an NHS clinical genetics laboratory on all PS-arm volunteers and only those FH-arm volunteers fulfilling standard FH-based criteria. These clinical/FH criteria have been described earlier and are given in the Supplementary material (Table S1).[14] *BRCA*-mutation-positive (and an equivalent number of randomly selected *BRCA*-mutation-negative) individuals received their result at standard face-to-face post-test

counselling. *BRCA* carriers were referred to an NHS regional genetics clinic for further management. Most *BRCA*-mutation-negative volunteers obtained test results by mail. *BRCA* founder-mutation-negative participants who had strong family histories of cancer fulfilling standard non-AJ high-risk criteria were also advised referral to genetic clinics.

GCaPPS Phase 1 was powered to assess psychological outcomes. A sample size of 509 per arm had 90% power to detect a difference of 1.2 points in total Hospital Anxiety-&-Depression Scale (HADS) scores between the two groups assuming a common SD of 5.9 and $\alpha = 0.05$. We report on long-term (up to 3 years) outcomes for (i) psychological health, (ii) quality of life and (iii) mutation rate. Customised questionnaires were used to collect sociodemographic and FH data. Validated questionnaires were used to assess psychological and quality-of-life outcomes as follows – Anxiety & Depression: HADS;[22] Quality of Life: SF12-questionnaire (Physical-Health Component scale and Mental-Health Component scale);[23] Health-Anxiety: very-short Health-Anxiety Inventory (HAI),[24]; Impact of genetic-test result disclosure: Multidimensional-Impact of Cancer-Risk-Assessment (MICRA) questionnaire (distress, uncertainty and positive-experience scales).[25] Data were collected at baseline (pre-counselling) and annually for 3 years post-result. FH-negative FH-arm participants were offered *BRCA* testing at the end of the study after 3 years of follow up.

Statistical analysis

Descriptive statistics were used for baseline characteristics. The primary comparison of outcomes involves an intention-to-treat analysis between the PS and FH arms. As outcome data are collected over multiple time-points, we modelled the results using random effects for HADS (including subscales 'anxiety' and 'depression'), MICRA (including subscales 'distress', 'uncertainty' and 'positive-experience'), SF12 (including subscales 'physical' and 'mental') and HAI. Each scale/subscale was analysed assuming the outcome as a continuous response variable. The responses to the scales at the time-points 'baseline', 1 year, 2 years and 3 years were analysed using linear mixed models, where a random-intercept term represented the unexplained heterogeneity corresponding to each participant. Each time-point was included as a fixed effect and interacted with the group term ('family history' or 'population screening') resulting in all eight group-by-time mean values being freely estimable, and reflecting individual group differences over time. In addition, the model was adjusted for gender (men versus women), marital status (married/cohabiting versus widowed/divorced/single), income (<£10,000, £10,000 to <£20,000, £20,000 to <£30,000, £30,000 to <£40,000, £40,000 to <£50,000 and >£50,000), education (degree-level/above versus no formal qualification/GCSE/O-level/CSE/NVQ1/NVQ2/A-level education), family history (low-risk versus high-risk) and age. The group-by-time interaction reflects potential differences over time between groups.

After modelling, we considered two specific predefined contrast tests (each on three degrees of freedom). First, we assessed a time effect for each group (specifically whether the mean value at time-points 1, 2 and 3 years were jointly different from the baseline level), and second, we assessed group differences adjusted for any baseline difference (whether the mean group differences value at time-points 1, 2 and 3 years were jointly different from the baseline group difference). This latter test was to establish whether the effect of PS could be deemed as detrimental compared with the FH modality by any outcome measure. Potential group differences over the four time-points were also explored visually, to help interpret the model parameters for group when interacted with time. STATA's margin command was used to make mean predictions over the sample for each of the eight group-by-time interactions. These marginal predictions, and their confidence intervals, were then plotted. Statistical analyses used STATA-11.0 (StataCorp LP, College Station, TX, USA). Two-sided *P*-values are reported for all statistical tests.

Funding

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Core Outcome Sets: There are no Core Outcome Sets for population or *BRCA* testing at present.

Patient and Public Involvement: During the development of the GCaPPS study a wide-ranging process of engagement was undertaken with all sections of the Jewish community.[11] This lasted a year. This included representatives from the Orthodox, Liberal, Reform, Masorti as well as the Unaffiliated sections of the community. It included a number of religious leaders, Rabbis and representatives, Jewish Charities, the Beth Din and stakeholders from the medical community. Also involved were cancer charities and patient support groups. This exercise enabled the exchange of ideas and understanding of underlying concerns or issues resulting from *BRCA* testing and conduct of the research. It provided community inputs into study protocol development, communication strategy, development of participant/patient-facing materials, study conduct/delivery and representation on governance committees. It generated support and awareness for the study. Delivery and completion of the study would not have been possible without it.

Results

A total of 1168 volunteers underwent pre-test counselling, of whom 1042 (89%) consented to *BRCA* testing over a 2-year recruitment period. Eight elected to withdraw from the study within the 3-week window, so 1034 (691 women, 343 men) were randomised to the PS ($n = 530$) or FH ($n = 504$) arms. The Consort flow-chart is given in Figure 1. A further 17 participants (PS arm, $n = 10$; FH arm, $n = 7$) withdrew during the follow-up period. Reasons provided included: death of spouse ($n = 1$), death ($n = 2$), relocation ($n = 1$), changed mind ($n = 4$), not wanting to complete questionnaires ($n = 4$), no longer relevant ($n = 2$), none ($n = 3$). The PS and FH arms were comparable at baseline in terms of age, gender, marital-status, children, income, education, Jewish affiliation and FH of cancer. These baseline characteristics have been described earlier and are given in the Supplementary material (Table S2).[14] The questionnaire response rate was 99% at baseline, 77–80% at 1 year, 71–72% at 2 years and 64–71% at 3 years (Figure 1).

Values for all outcome scales (anxiety, depression, health-anxiety, physical/mental quality-of-life, distress, uncertainty and positive-experience) by group over time are given in Table 1. Contrast tests to assess the joint effect of difference in these outcomes between FH and PS groups over time (Table 2) showed a statistically significant decrease in anxiety ($P = 0.046$) and overall HADS ($P = 0.0.012$) scores in the PS arm compared with the FH arm over 3 years (Table 2, Figure 2). There was no statistically significant difference in depression scores between the PS and FH groups over time (Table 2, Figure 2). Overall, anxiety within both PS ($P < 0.0005$) and FH ($P = 0.018$) groups decreased over time, whereas the total HADS scores decreased over time in the PS arm alone ($P < 0.0005$) (Tables 1 and 2; Figure 2). There was a small increase in depression scores over time within the FH group ($P = 0.035$) but not within the PS group (Tables 1 and 2). There was no statistically significant difference in overall quality-of-life or physical/mental quality-of-life scores between the PS and FH arms over time (Table 2; and see Supplementary material, Figure S1). However, there was a small significant decrease in overall quality-of-life scores seen in both the FH ($P = 0.005$) and PS ($P = 0.004$) groups over 3 years (Table 2). Though statistically significant, the absolute decrease is extremely small (change in score from ~101 to 100), not clinically meaningful and consistent with decreasing physical quality of life seen with

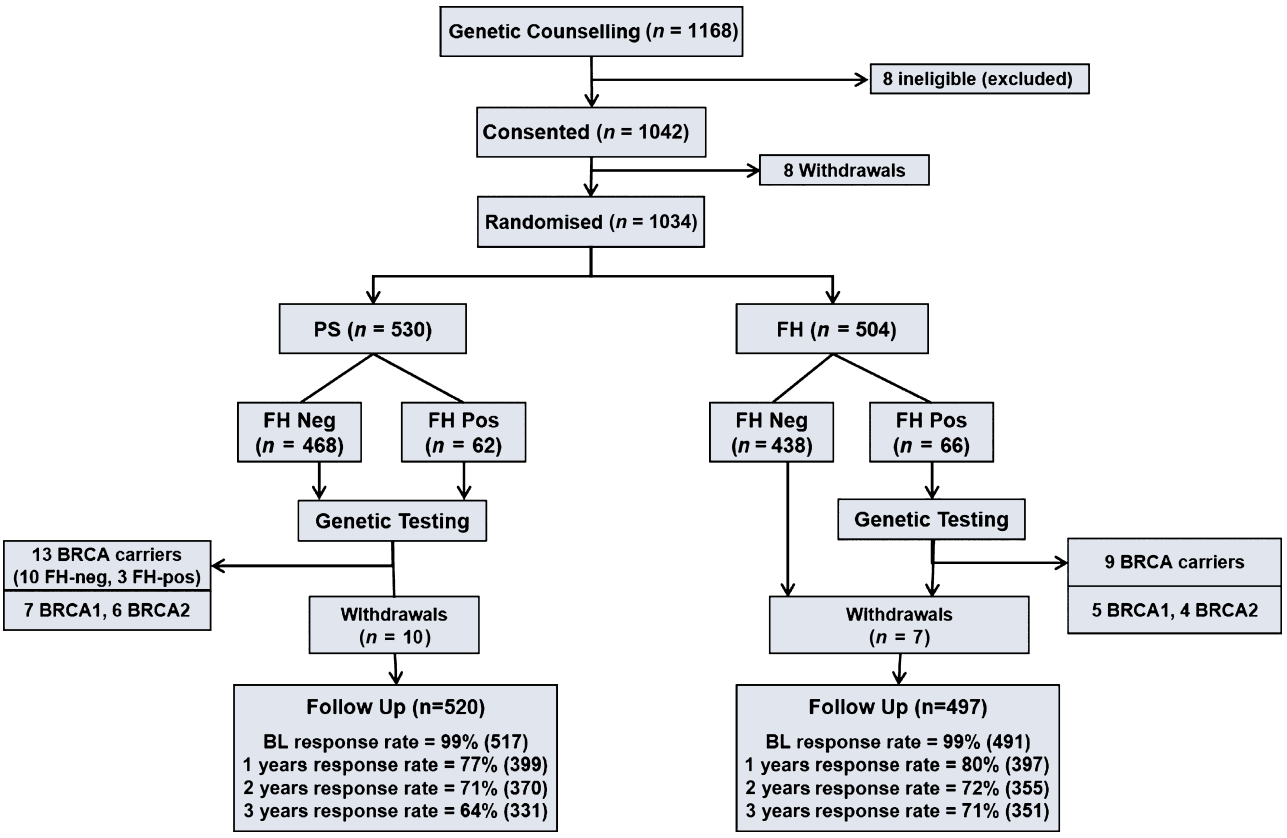

Figure 1. Consort flow chart for the study. BL, baseline; FH, family history; Neg, negative; PS, population screening; Pos, positive; yr, year.

Table 1. Psychological and quality-of-life outcome scores by group

	Mean scores (standard error)	FH (n = 504)	PS (n = 530)
HADS	HADS total baseline (SE)	9.2 (0.25)	8.7 (0.25)
	HADS total 1 year (SE)	8.9 (0.27)	7.7 (0.26)
	HADS total 2 years (SE)	9.1 (0.28)	7.9 (0.27)
	HADS total 3 years (SE)	9.3 (0.28)	7.8 (0.28)
	HADS anxiety baseline (SE)	6.2 (0.16)	5.96 (0.16)
	HADS anxiety 1 year (SE)	5.8 (0.17)	5.2 (0.17)
	HADS anxiety 2 years (SE)	5.8 (0.18)	5.2 (0.17)
	HADS anxiety 3years (SE)	6 (0.18)	5.1 (0.18)
	HADS depression baseline (SE)	2.9 (0.13)	2.7 (0.12)
	HADS depression 1 years (SE)	3.1 (0.13)	2.5 (0.13)
	HADS depression 2 years (SE)	3.2 (0.14)	2.7 (0.13)
	HADS depression 3 years (SE)	3.3 (0.14)	2.6 (0.14)
SF12	SF12 total-scale baseline (SE)	101.2 (0.32)	101.8 (0.31)
	SF12 total scale 1 year (SE)	100.2 (0.34)	100.9 (0.34)
	SF12 total scale 2 years (SE)	100.1 (0.36)	100.6 (0.35)
	SF12 total scale 3 years (SE)	100.3 (0.36)	100.9 (0.36)
	SF12 physical scale BASELINE (SE)	49.1 (0.24)	49.4 (0.23)
	SF12 physical scale 1 year (SE)	48.9 (0.26)	48.6 (0.26)
	SF12 physical scale 2 years (SE)	48.8 (0.27)	48.5 (0.26)
	SF12 physical scale 3years (SE)	48.7 (0.27)	48.5 (0.27)
	SF12 mental scale baseline (SE)	52 (0.26)	52.4 (0.25)
	SF12 mental scale 1 year (SE)	51.3 (0.28)	52.3 (0.28)
	SF12 mental scale 2 years (SE)	51.3 (0.30)	52 (0.29)
	SF12 mental scale 3 years (SE)	51.6 (0.30)	52.4 (0.30)
HAI	vsHAI score baseline (SE)	3.2 (0.13)	3.1 (0.13)
	vsHAI score 1 year (SE)	2.6 (0.13)	2.5 (0.13)
	vsHAI score 2 years (SE)	2.4 (0.13)	2.3 (0.13)
	vsHAI score 3 years (SE)	2.4 (0.13)	2.1 (0.13)
MICRA	MICRA distress score 7 days (SE)	1.53 (0.34)	0.82 (0.14)
	MICRA distress score 1 year (SE)	1.02 (0.22)	0.63 (0.15)
	MICRA distress score 2 years (SE)	1.07 (0.23)	0.73 (0.15)
	MICRA distress score 3 years (SE)	0.63 (0.27)	0.63 (0.16)
	MICRA uncertainty score 7 days (SE)	3.8 (0.57)	2.9 (0.24)
	MICRA uncertainty score 1 year (SE)	3.5 (0.39)	2.5 (0.25)
	MICRA uncertainty score 2 years (SE)	3.2 (0.40)	2.6 (0.26)
	MICRA uncertainty score 3 years (SE)	2.9 (0.46)	2.7 (0.27)
	MICRA positive experiences score 7 days (SE)	6.9 (0.94)	6.1 (0.36)
	MICRA positive experiences score 1 year (SE)	10.8 (0.6)	11.0 (0.39)
	MICRA positive experiences score 2 years (SE)	12.4 (0.61)	11.8 (0.39)
	MICRA positive experiences score 3 years (SE)	12.4 (0.72)	11.6 (0.42)

Joint contrasts of marginal linear prediction over time. Baseline value is the reference value. Mean outcome values are adjusted for other covariates: gender, age, education, income, family history, marital status.

increasing age in population-level data. *BRCA* testing was associated with an overall decrease in health-anxiety within both groups over time ($P < 0.0005$); however, no significant difference in health-anxiety was observed between FH- and PS-based testing over time (Tables 1 and 2; Figure 2). There was no statistically significant long-term difference in distress, uncertainty or positive-experience scores between FH and PS approaches to *BRCA* testing (Table 2; and see Supplementary material, Figure S2). Contrast tests did not show a decrease/change in distress or uncertainty associated with *BRCA* testing within the groups over long-term follow up (Table 2; and see Supplementary material, Figure S2). Both groups showed a similar increase in positive-experience scores over time ($P < 0.005$) (Table 2). These results indicate that there is no evidence that population-based *BRCA* testing has any detrimental/adverse psychological or quality-of-life effects compared with an FH-based approach over the long-term. There is some evidence of potential benefit with lower long-term anxiety and HADS scores with population-based *BRCA* testing compared with FH-based testing.

Linear mixed models outputs showing the association of covariates with the different outcomes are given in the Supplementary material (Table S3). Higher income was significantly associated with lower levels of anxiety ($P < 0.0005$), depression ($P < 0.005$), health-anxiety ($P = 0.02$), distress ($P < 0.005$) and uncertainty ($P = 0.003$), and higher quality-of-life scores ($P < 0.005$) with genetic testing (see Supplementary material, Table S3). Overall, men (compared with women) had lower levels of

anxiety ($P < 0.0005$) and health-anxiety ($P = 0.001$), and higher quality-of-life ($P < 0.005$) and positive-experience ($P < 0.005$) scores. Higher education was associated with lower mental quality-of-life ($P = 0.004$) scores and lower levels of post-testing distress ($P = 0.006$) and uncertainty ($P = 0.007$) (see Supplementary material, Table S3). A strong FH of cancer (FH-positive) was associated with higher depression scores ($P = 0.025$) but not with any other outcome variables (see Supplementary material, Table S3). Increasing age was associated with increased depression scores ($P = 0.01$) but lower anxiety levels ($P < 0.005$), lower positive-experience scores ($P < 0.005$) and lower physical quality-of-life scores ($P < 0.0005$), but higher mental quality-of-life scores ($P < 0.0005$) (see Supplementary material, Table S3).

Five hundred and thirty participants in the PS arm and 66 in the FH arm underwent *BRCA* testing. Thirteen carriers (seven *BRCA1*, six *BRCA2*) were detected in the PS arm, of whom three were FH-positive. Nine carriers (five *BRCA1*, four *BRCA2*) were detected in the FH arm.[14] Following completion of the study, at 3-year follow up, all FH-negative volunteers in the FH arm were offered *BRCA* testing. At the time of our last report,[14] FH-negative volunteers in the FH arm had not completed *BRCA* testing. We identified three additional *BRCA* carriers among them. Thus, 438 FH-negative volunteers in the FH arm underwent *BRCA* testing after completing their 3-year follow up making it a total of eight *BRCA* carriers in the FH-negative FH-arm sub-group. Hence, the total *BRCA* prevalence in the cohort is 30/1034 (2.9%; 95% CI 1.97–4.12%). Of these, 18 (60%) did not fulfil clinical criteria for *BRCA* testing and would not have been detected by FH alone. The overall prevalence for *BRCA1* was 1.55% (95% CI 0.89–2.5%) and for *BRCA2* was 1.35% (95% CI 0.74–2.26%). The combined *BRCA* prevalence in FH-positive individuals from both arms was 9.4% (95% CI 4.9–15.8%) and prevalence in FH-negative individuals was 1.99% (95% CI 1.2–3.1%).

Discussion

Main findings

To the best of our knowledge, GCaPPS remains the only RCT comparing unselected population-based and FH/clinical-criteria-driven approaches with *BRCA* testing. We found no statistically significant long-term difference in levels of depression, health-anxiety, distress, uncertainty and overall quality of life when directly comparing population-based and FH/clinical-criteria-based approaches to *BRCA* testing in AJ individuals. Of the decrease in anxiety, uncertainty and distress with *BRCA* testing seen initially on short-term follow up,[14] only a decrease in anxiety was maintained over the long term. Additionally, population-based *BRCA* testing had the advantage/benefit of being associated with a significantly greater reduction in long-term anxiety and overall anxiety-&-depression (HADS) scores compared with FH-based *BRCA* testing. Although this decrease was statistically significant, the effect size is small (Table 1) and probably unlikely to be clinically meaningful. Nevertheless, the overall long-term decrease in anxiety and health anxiety associated with population-based *BRCA* testing is reassuring and consistent with earlier findings reporting psychological benefits associated with *BRCA* testing in high-risk women.[26–28] However, no change in short-term anxiety was reported in the Israeli population-cohort study over 6 months of follow up.[16]

Strengths and weaknesses

The strengths of our study include the randomised design, pre-test counselling, use of validated questionnaires, involving both men and women, long-term follow up, and good questionnaire response rates. Weaknesses include the lack of qualitative data. However, qualitative data from an Israeli study[29] are supportive of population testing and complement the quantitative findings from our study and other studies. Findings from our study are limited to the Jewish population. Levels of income and education in the Jewish population (and our study participants) are higher than in the wider UK general population. Socio-cultural differences exist between the Jewish and non-Jewish populations. Study outcomes with respect to impact on psychological health and quality of life therefore cannot be directly extrapolated to the non-Jewish general population and generalisability beyond the Jewish population is limited. Applicability of such an approach to the general non-AJ population requires more research.

Interpretation

Our results are reassuring as they reconfirm that the lack of adverse short-term consequences to psychological health and quality of life from population testing seen at 3 months[14] are maintained over the long term. Although we did not find a difference in cancer-related distress or uncertainty between FH- and PS-testing approaches, increased levels of distress have been reported in mutation carriers in two population-cohort studies at up to 1 year post-test results.[16,17] However, these studies lacked a current-practice comparator control arm and their findings are similar to outcomes from testing high-risk women.[18,20] The increase in positive-experience scores seen at short-term follow up[14] persisted over the long term. This could reflect reducing family support or relief with the passage of time following receipt of the test result. The small decrease in quality-of-life scores found with time is consistent with normative data showing a decrease in quality of life with age[30,31] and the lack of difference observed between the

Table 2. Contrast tests for between-group and within-group analyses over time

HADS-total	**df**	χ^2	***P*-value**	**SF12 Total scale**	**df**	χ^2	***P*-value**
Year#Group				Year#Group			
BL vs Year-1 (joint)	1	5.81	0.016	BL vs Year-1 (joint)	1	0.1	0.747
BL vs Year-2 (joint)	1	4.25	0.039	BL vs Year-2 (joint)	1	0.04	0.836
BL vs Year-3 (joint)	1	9.22	0.002	BL vs Year-3 (joint)	1	0	0.981
BL vs overall (joint)	3	10.9	0.012	BL vs Overall (joint)	3	0.26	0.968
Year|Group				Year|Group			
BL vs joint |FH	3	2.21	0.529	BL vs Joint |FH	3	12.81	0.005
BL vs joint |PS	3	26.19	<0.0005	BL vs Joint |PS	3	13.3	0.004
HADS-anxiety	**df**	χ^2	***P*-value**	**SF12 Physical scale**	**df**	χ^2	***P*-value**
Year#Group				Year#Group			
BL vs Year-1 (joint)	1	3.65	0.056	BL vs Year-1 (joint)	1	1.7	0.192
BL vs Year-2 (joint)	1	3.65	0.06	BL vs Year-2 (joint)	1	1.69	0.193
BL vs Year-3 (joint)	1	6.93	0.009	BL vs Year-3 (joint)	1	1.4	0.237
BL vs overall (joint)	3	8.03	0.046	BL vs Overall (joint)	3	2.58	0.46
Year|Group				Year|Group			
BL vs joint |FH	3	10.06	0.018	BL vs Joint |FH	3	2.48	0.478
BL vs joint |PS	3	46.84	<0.0005	BL vs Joint |PS	3	14.29	0.002
HADS-depression	**df**	χ^2	***P*-value**	**SF12 Mental scale**	**df**	χ^2	***P*-value**
Year#Group				Year#Group			
BL vs year-1 (joint)	1	4.82	0.028	BL vs Year-1 (joint)	1	2.4	0.122
BL vs year-2 (joint)	1	2.4	0.121	BL vs Year-2 (joint)	1	0.83	0.362
BL vs year-3 (joint)	1	6.15	0.013	BL vs Year-3 (joint)	1	1.16	0.281
BL vs overall (joint)	3	7.71	0.052	BL vs Overall (joint)	3	2.69	0.454
Year|Group				Year|Group			
BL vs joint |FH	3	8.6	0.035	BL vs Joint |FH	3	8.67	0.034
BL vs joint |PS	3	3.58	0.311	BL vs Joint |PS	3	2.62	0.576
HAI	**df**	χ^2	***P*-value**	**Micra-distress**	**df**	χ^2	***P*-value**
Year#Group				Year#Group			
BL vs year-1 (joint)	1	0.1	0.751	BL vs Year-1 (joint)	1	0.73	0.397
BL vs year-2 (joint)	1	0.02	0.883	BL vs Year-2 (joint)	1	0.96	0.327
BL vs year-3 (joint)	1	2.19	0.139	BL vs Year-3 (joint)	1	3.25	0.071
BL vs overall (joint)	3	3.27	0.352	BL vs Overall (joint)	3	3.47	0.325
Year|Group				Year|Group			
BL vs joint |FH	3	54.6	<0.0005	BL vs Joint |FH	3	6.42	0.093
BL vs joint |PS	3	79.22	<0.0005	BL vs Joint |PS	3	2.26	0.521
Micra pos-experience	**df**	χ^2	***P*-value**	**MICRA uncertainty**	**df**	χ^2	***P*-value**
Year#Group				Year#Group			
BL vs year-1 (joint)	1	1.03	0.31	BL vs Year-1 (joint)	1	0.15	0.694
BL vs year-2 (joint)	1	0.1	0.755	BL vs Year-2 (joint)	1	0.09	0.77
BL vs year-3 (joint)	1	0	0.968	BL vs Year-3 (joint)	1	0.96	0.327

Table 2. (Continued)

Micra pos-experience	df	χ^2	*P*-value	MICRA uncertainty	df	χ^2	*P*-value
BL vs overall (joint) Year|group	3	1.81	0.613	BL vs Overall (joint) Year|Group	3	2.94	0.401
BL vs joint |FH	3	35.03	<0.0005	BL vs Joint |FH	3	2.85	0.416
BL vs joint |PS	3	256.9	<0.0005	BL vs Joint |PS	3	4.37	0.224

BL, baseline; df, degrees-of-freedom; FH, family history; HADS, hospital anxiety-&-depression scale; HAI, health-anxiety inventory; MICRA, Multidimensional-Impact of Cancer-Risk-Assessment; Pos, positive; PS, population screening; SE, standard-error.
'Year#Group', refers to the group–time interaction, which reflects the between-group difference over time. BL vs Year-1 (joint), BL vs Year-2 (joint), BL vs Year-3 (joint), reflect whether mean group difference at each time-point (year-1, year-2, or year-3, respectively) was different from baseline. BL vs Overall (joint), reflects whether the mean group differences value at time-points 1, 2 and 3 years were together jointly different from the baseline group difference. Year|Group, refers to the group–time interaction, which reflects the within-group difference over time. BL vs Joint |FH, reflects whether the outcome scale value at time-points 1, 2 and 3 years were together jointly different from the baseline within the family-history group. BL vs Joint |PS, reflects whether the outcome scale value at time-points 1, 2 and 3 years were together jointly different from the baseline within the population-screening group.

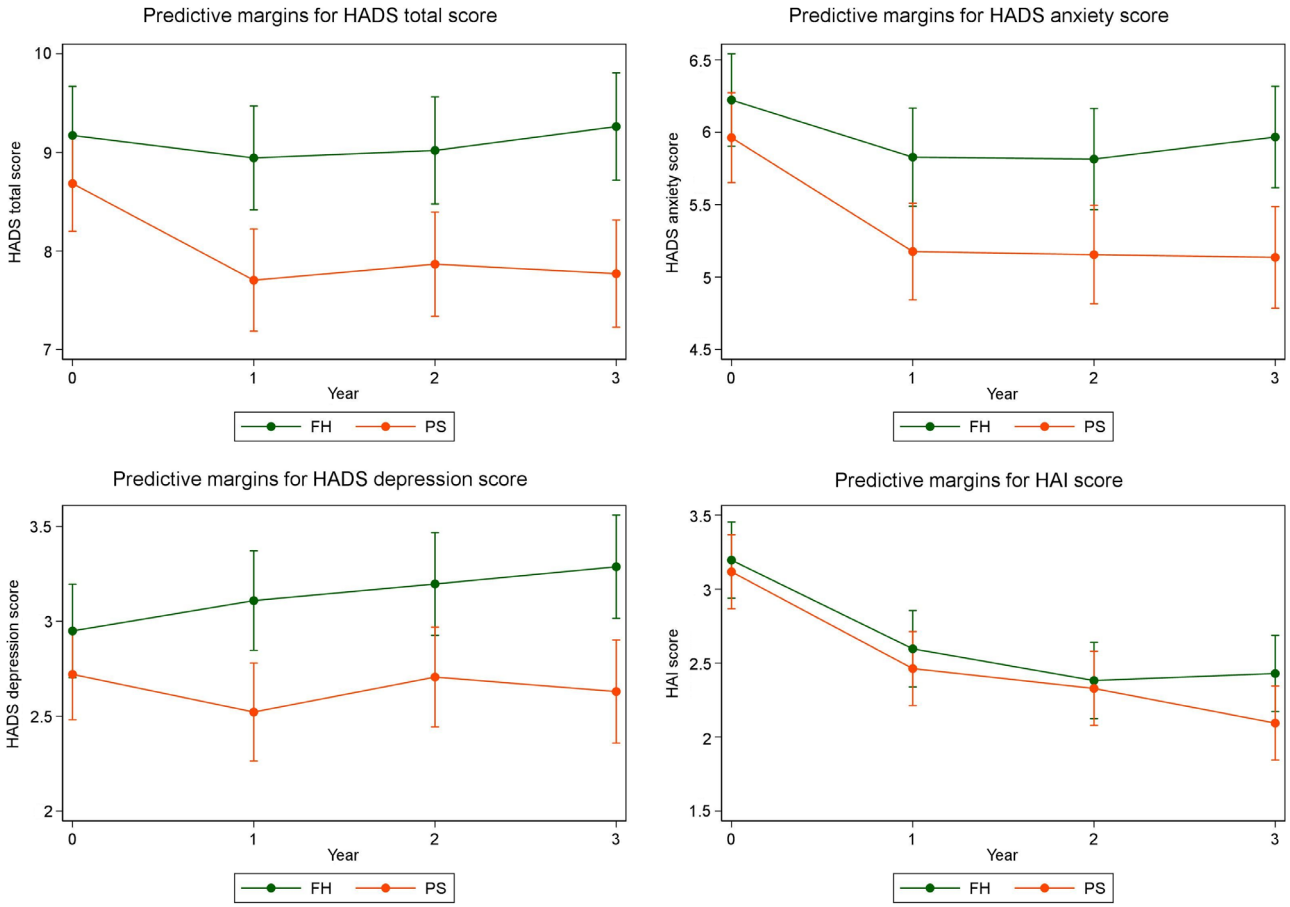

Figure 2. Anxiety, depression and health-anxiety outcomes by group over time. FH, family history; HADS, hospital anxiety and depression scale; HAI, health-anxiety inventory; PS, population-screening. Shows the change in HADS-anxiety, HADS-depression, Total-HADS and HAI scores between FH and PS groups over time.

two *BRCA*-testing approaches is reassuring. The baseline distribution of anxiety, depression[32] and quality-of-life[31,33] scores in our cohort is similar to that found in normative UK-population data.[34] Having a strong FH of cancer was associated with higher depression scores across the cohort but not any outcome measures assessed. Both increased distress[35] and no adverse psychological consequences[36] have been reported earlier in high-risk Jewish women following genetic testing.

There are several differences between GCaPPS and the two single-arm Israeli and Canadian population studies, including a randomised design, provision of pre-test counselling before *BRCA* testing (in addition to post-test counselling) and inclusion of both women and men in our study. Twenty percent of Canadian participants (and 50% *BRCA* carriers) who received only post-test counselling following population-based *BRCA* testing expressed a preference for pre-test counselling after receiving their results.[17] Nevertheless, high satisfaction levels (91–93%) have been reported with population-based *BRCA* testing in the Canadian and Israeli studies on quantitative[16,17] and qualitative[29] analysis. Pre-test genetic counselling undertaken in our study offered the opportunity to explore complexities and limitations around risk estimation incorporating an individual's family-history and demographic variables as well as address any specific issues related to *BRCA* testing before undergoing genetic testing.[11] This affected decision-making[11] and remains part of current standard clinical guidelines before genetic testing.[37] The Israeli and Canadian studies successfully implemented a model of large-scale *BRCA* testing without pre-test counselling. An ongoing US study is also using that approach with a web-based consent process.[38] A pilot UK study has shown the feasibility/acceptability of a web-based decision-aid plus telephone helpline for consent and recruitment to population-based genetic testing.[39] There are currently no randomised-trial data comparing population-based *BRCA* testing with and without pre-test counselling. As access to testing broadens on a population basis the newer more time/cost-efficient approaches to consenting for genetic testing will need robust evaluation (in randomised trials) to establish effectiveness and non-inferiority/equivalence to the more established standard counselling approaches.

The slightly higher income and education levels seen in our study participants are consistent with the income/education levels found in the UK Jewish population compared with the general population. The significant associations of some study outcome variables seen with demographic variables of income, gender, age and education are largely consistent with observations from population-based data reported in other population cohorts. Importantly, a number of these findings could relate to the large sample size and in view of the small effect sizes, are unlikely to be clinically important.

The overall 2.9% *BRCA* prevalence is marginally higher but well within the confidence intervals of other reports.[40–42] Our finding of high *BRCA* prevalence in FH-negative individuals and 60% of *BRCA* carriers lacking clinical criteria for testing is similar to other studies that reported this to range from 40 to 63%.[40–42] Potential reasons for absence of FH include, small family size, paternal transmission, male preponderance, few women inheriting the mutation, poor communication and chance. Our data coupled with other reports clearly illustrate the limitations of a clinical-threshold/criteria-based approach over unselected population-based *BRCA* testing.

Most of our healthcare structure and ongoing research is predominantly aimed towards disease diagnosis/treatment rather than illness prevention. There is a huge opportunity for the health system to use advances in technology and bioinformatics to maximise identification of mutation carriers/high-risk individuals who can benefit from consequent cancer screening and prevention. The traditional approach to *BRCA* testing uses an *a priori* FH-based probability threshold and misses many *BRCA* carriers. Individuals in the family need to develop cancer before unaffected relatives can be identified. It requires awareness of FH and its importance by family members and the GP/health professional. This gate-keeper approach restricts access, delays identification of unaffected individuals, and is associated with under-utilisation of genetic testing.[8,10] We found that only 3% of general and 11% of AJ *BRCA* carriers have been identified in a 16-million population across Greater London.[9] It is likely that a similar picture exists across most parts of the western hemisphere. The current system is failing to achieve the maximum/full potential for genetic cancer prevention, and highlights the need to explore other strategies.

Next-generation-sequencing technologies,[43,44] falling costs and advances in computational bioinformatics make population testing feasible. The rapidly changing genomic landscape, improved genetic understanding of disease and increasing awareness offer a massive opportunity to apply this knowledge and technology on a broad population scale to make an important shift in health care towards disease prevention. GLOBOCAN data suggest that OC/BC incidence will increase by 24%/27% in the UK and by 55%/55% worldwide over the next 20 years.[45] Poor OC survival rates and effective options available for BC and OC prevention in high-risk women highlight the acute need for using population genomics to maximise cancer prevention. Our data[12–15,46] coupled with other reports from the literature[16,17,29,40,42] strongly support a change in paradigm and implementation of population-based *BRCA* testing in the Jewish population. This will need to be accompanied by context-specific expansion in genetics and downstream management infrastructure along with development of

logistics and implementation pathways in a planned and organised manner. Recent data suggest that genetic testing for BC/OC gene mutations could be cost-effective in general-population women too,[47] but additional research, including general-population implementation studies, is needed to address knowledge gaps before that step can be considered.

Chronic disease is a major public health burden. The Centers for Disease Control and Prevention reports the top five causes of deaths as: (i) heart disease, (ii) cancer, (iii) lung disease, (iv) accidents and (v) strokes.[48] Fifty percent of adults have at least one and 25% of adults have two or more chronic health conditions and the latter accounts for >90% of Medicare expenditure. In England chronic conditions account for 50% of GP appointments, 64% of outpatient appointments, 70% of inpatient bed-days and 70% of the total healthcare spend.[49] The increasing prevalence of long-term/chronic conditions (including cancer) is the biggest challenge facing the health system.[49] A population-testing approach provides opportunity for exploring strategic change by nudging the needle of health care towards prevention. Population-based *BRCA* testing in the Jewish population provides the first model to explore population genomics for preventing chronic disease.

Conclusion

Population-based *BRCA* testing in the Jewish population does not adversely affect long-term psychological wellbeing or quality of life and is associated with decreased anxiety compared with FH/criteria-based testing. It identifies many more *BRCA* carriers, is acceptable, feasible, safe and even cost-saving. It provides the first implementable model for the application of population genomics for cancer prevention. We call for a change in guidelines to reflect this.

Disclosure of interest

IJ and UM have a financial interest in Abcodia, Ltd, a company formed to develop academic and commercial development of biomarkers for screening and risk prediction. IJ is a member of the board of Abcodia Ltd, a Director of Women's Health Specialists Ltd and received consultancy from Becton Dickinson. RM declares research funding from The Eve Appeal and Cancer Research UK into population testing and from Barts & the London Charity and Rose Trees Trust outside this work, an honorarium for grant review from the Israel National Institute for Health Policy Research and an honorarium for advisory board membership from Astra Zeneca/MSD. RM is supported by an NHS Innovation Accelerator (NIA) Fellowship for population testing. The other authors declare no conflict of interest. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

Conception: RM, IJ. Design and development: RM, IJ and UM. Questionnaire development: RM, IJ, UM, JW, SS, KL, SG. Data collection: RM, RD, KL. Data analysis: MB, RM. Preparation of tables and figures: RM, MB, FG. Trial management: RM, IJ, UM, KL, RD, JW, SG, LS, HD, YW, CC, IT, UB, AB. Genetic testing: YW. Data collection from Guys genetic laboratories: CJ. Initial draft of manuscript: RM, FG, MB. Manuscript writing, review and approval: all authors.

Details of ethics approval

The GCaPPS study received full ethics approval from the Institute of Child Health/Great Ormond Street Hospital Research Ethics Committee on 8 June 2008 (REC Reference number 08/H0713/44). The study was registered with the International Standard Randomized Controlled Trial Number Register – ISRCTN 73338115 (http://www.controlled-trials.com/ISRCTN73338115).

All trial volunteers provided written informed consent to participate in the study.

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Data sharing

Relevant anonymised data can be obtained on reasonable request from the corresponding author on completion of secondary analyses, which are ongoing.

Supporting Information

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

Figure S1. SF12 quality-of-life scores by group over time.

Figure S2. MICRA uncertainty, distress and positive experience scores by group over time.

Table S1. High-risk criteria.

Table S2. Baseline characteristics of population-screening and family-history arms.

Table S3. Linear mixed models for study outcomes.

Video S1. Author Insights. ■

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