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Article

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Population Testing for Cancer Predisposing BRCA1/BRCA2 Mutations in the Ashkenazi-Jewish Community: A Randomized Controlled Trial

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Abstract

Background: Technological advances raise the possibility of systematic population-based genetic testing for cancer-predisposing mutations, but it is uncertain whether benefits outweigh disadvantages. We directly compared the psychological/quality-of-life consequences of such an approach to family history (FH)–based testing.

Methods: In a randomized controlled trial of BRCA1/2 gene-mutation testing in the Ashkenazi Jewish (AJ) population, we compared testing all participants in the population screening (PS) arm with testing those fulfilling standard FH-based clinical criteria (FH arm). Following a targeted community campaign, AJ participants older than 18 years were recruited by self-referral after pretest genetic counseling. The effects of BRCA1/2 genetic testing on acceptability, psychological impact, and quality-of-life measures were assessed by random effects regression analysis. All statistical tests were two-sided.

Results: One thousand, one hundred sixty-eight AJ individuals were counseled, 1042 consented, 1034 were randomly assigned (691 women, 343 men), and 1017 were eligible for analysis. Mean age was 54.3 (SD = 14.66) years. Thirteen BRCA1/2 carriers were identified in the PS arm, nine in the FH arm. Five more carriers were detected among FH-negative FH-arm participants following study completion. There were no statistically significant differences between the FH and PS arms at seven days or three months on measures of anxiety, depression, health anxiety, distress, uncertainty, and quality-of-life. Contrast tests indicated that overall anxiety ($P = .0001$) and uncertainty ($P = .005$) associated with genetic testing decreased; positive experience scores increased ($P = .0001$); quality-of-life and health anxiety did not change with time. Overall, 56% of carriers did not fulfill clinical criteria for genetic testing, and the BRCA1/2 prevalence was 2.45%.

Conclusion: Compared with FH-based testing, population-based genetic testing in Ashkenazi Jews doesn't adversely affect short-term psychological/quality-of-life outcomes and may detect 56% additional BRCA carriers.

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Important advances in understanding germ-line predisposition to familial cancer have led to the identification of several rare high-penetrance genes causing cancer syndromes: BRCA1/BRCA2 (familial breast and/or ovarian cancer) and mismatch-repair genes (Lynch Syndrome). BRCA1/2 carriers have a 50% to 80% risk of breast cancer, a 20% to 45% risk of ovarian cancer (OC), and a 5% to 25% risk of prostate cancer (1–5). Established management strategies for high-risk individuals include: 1) risk-reducing salpingo-oophorectomy (RRSO) to prevent tubal/ovarian cancer (hazard ratio [HR] = 0.21) (which also halves breast cancer risk in premenopausal women) (6), 2) risk-reducing mastectomy to prevent breast cancer (7–9), 3) early onset breast screening (MRI/mammograms), and 4) preimplantation genetic diagnosis.

Within the UK National Health Service (NHS), genetic mutation testing is limited to individuals with cancer from high-risk families (carrier probability ≥20% in the general population and ≥10% in the Jewish population) or individuals from families with a confirmed BRCA mutation who request referral to specialist genetic clinics. This family history (FH)–based approach requires individuals/general practitioners to recognize and act on a clinically significant FH. Mutation carriers who lack/are unaware of their FH, who do not recognize the risk associated with FH or are not proactive in seeking advice, are inevitably excluded (10–12). Most of these current approach–associated limitations could be overcome by systematic population-based testing. The literature indicates that genetic counseling/testing is associated with psychological benefits in noncarriers and has no substantial adverse psychological consequences for carriers (8,13). However, available data are predominantly from trials in highly selected samples of individuals with a strong FH of cancer, and the results cannot be generalized to the general population. There is no established model for population-based testing of dominant mutations, and the best way to deliver this service on a population basis is unknown.(13)

We describe results from the first phase of a novel randomized controlled trial (RCT), Genetic Cancer Prediction through Population Screening (GCaPPS). The objective was to assess the benefits/disadvantages of a population-based approach to genetic testing for high penetrance–dominant gene mutations compared with the conventional FH-based approach. The RCT design provided a basis for comparison of psychological and quality-of-life differences between population-based and FH-based testing. We based the trial in an Ashkenazi Jewish (AJ) community as a population-model and used BRCA1/2-mutations as our disease-model. These choices were guided by the higher prevalence of three BRCA1/2 founder mutations in the AJ population.

Methods

Design

GCaPPS is an RCT (ISRCTN73338115) with two arms: population-screening (PS) arm and family-history (FH) arm. Inclusion criteria were: age greater than 18 years and AJ ethnicity (self-reported history, four AJ grandparents). Exclusion criteria were: known BRCA mutation, first-degree relative (FDR) of a BRCA carrier or previous BRCA testing. This article reports on: 1) founder-mutations detected, 2) acceptability of the test, and 3) psychological and quality-of-life impact. Further analysis of uptake of screening/preventive strategies is in progress.

Participants

Participants were recruited via the North-London Jewish community, following a broad-based consultation with key stakeholders of the AJ community and publicity about the program.

Recruitment

Recruitment was by self-referral. Study information/leaflets were made available through community charities, religious groups, a pharmacy chain (Boots), and website (www.gcapps.org). Volunteers received structured, nondirective pretest genetic counseling for informed decision-making between October 2008 and July 2010 at six centers, which included a popular high street pharmacy chain and Jewish charity community centers, thus providing counseling within a novel high street/community-based setting. Genetic counseling was undertaken by a qualified genetic counselor with supervision from a Regional Genetics Centre and a clinical fellow with substantial experience in cancer genetics risk assessment and management. It was structured to meet the goals of genetic counseling and cancer risk assessment. FH and baseline data were collected at initial appointment. Individuals deciding to undergo genetic testing were consented postcounseling.

Randomization

Consenting participants were randomly assigned postcounseling using a computer generated random-number algorithm. Genetic counselors were blinded to group allocation during counseling and recruitment. Participants were informed of their randomly assigned allocation by mail.

Genetic Analysis

Genetic testing was performed on all PS-arm volunteers and only FH-arm volunteers fulfilling standard FH-based criteria (Table 1). This involved sequencing analysis of BRCA1 exons 1 and 20 and a segment of BRCA2 exon 11 for three Jewish founder mutations: 185delAG(c.68_69delAG), 5382insC(c.5266dupC), and 6174delT(c.5946delT) in an NHS clinical genetics laboratory. Variants detected were reconfirmed using a separate aliquot of the original DNA sample. We also obtained data on AJ BRCA carriers detected through London clinical genetics laboratories from 2000 to 2010.

Test Result Management

Founder mutation–positive (and equivalent number of randomly selected founder mutation–negative) individuals received their result at standard face-to-face post-test counseling. Mutation carriers were advised to request referral (via general-practitioner) to an NHS regional genetics clinic for confirmatory testing and access to established risk-management services. Founder mutation–negative volunteers who fulfilled standard non-AJ high-risk criteria (Table 1) were also referred to genetic clinics. All other founder mutation–negative volunteers obtained test results by mail.

Assessment of Demographic, Psychosocial Outcomes, and Follow-up

Sociodemographic and FH data were collected using a customized questionnaire. Depression and anxiety were assessed with the Hospital Anxiety and Depression Scale (HADS) (14).

Table 1. High-risk criteria

AJ high-risk criteria for FH-positive group (used in clinical genetics units)
Volunteer should fulfill any one of the following criteria (volunteer/proband should either have been affected by cancer or be a first degree relative (FDR) of an affected family member)
1) FDR with breast cancer (<50 years)
2) FDR with ovarian cancer* (any age)
3) Personal history of breast cancer (<50 years)
4) Personal history of ovarian cancer* (any age)
5) FDR with MBC (any age)
6) Personal history (men) of MBC (any age)
* Equivalence of history of ovarian/PPC/FTC for HR criteria
Extended high-risk criteria for referral of FM-negative volunteers to the regional genetic units
Volunteer should fulfill any one of the following criteria (volunteer/proband should either have been affected by cancer or be a FDR of an affected family member; criteria should be fulfilled on the same side of the family)
Families with ovarian* cancer (HOC) or breast and ovarian* cancer (HBOC)
1) ≥2 individuals with ovarian cancer* who are FDR
2) 1 ovarian cancer* and 1 breast cancer <50 years who are FDR
3) 1 ovarian cancer* and 2 breast cancers <60 years who are FDR
4) Criteria 1, 2, and 3 can be modified where paternal transmission is occurring ie, families where affected relatives are related by second degree through an unaffected intervening male relative and there is an affected sister are eligible
5) Breast cancer in volunteer/proband (≤50 years) and mother (or sister) with both breast and primary ovarian cancer* (in the same person)
Families with breast cancer only (HBC)
6) Breast cancer in volunteer/proband (≤50 years) and any one of the following:
a) breast cancer in mother (age of onset being ≤30 years in one and ≤50 years in the other) or
b) b/l† breast cancer in mother or sister (≤50 years onset of first)
7) ≥4 breast cancers
8) 3 breast cancers related by FDR and
a) 1 ≤30 years or
b) 2 ≤40 years (and all ≤60 years) or
c) 1 MBC (≤60 years) and other 2 ≤50 years
Male breast cancer
9) 2 MBC (≤60 years) in the family, and proband is an FDR of 1 of them
Mutation-positive families
10) Known non-FM in the family
11) Known history of mutation in the family, though unable to trace/identify exact pathogenic mutation and testing negative for 3 FM

* Equivalence of history of ovarian/primary peritoneal cancer/ fallopian tube cancer for high-risk criteria. AJ = Ashkenazi Jewish; b/l = bilateral; FH = family history; FM = founder mutation; FTC = fallopian tube cancer; HR = high-risk; MBC = male breast cancer; PPC = primary peritoneal cancer.
† Cases of b/l breast cancer: Each breast cancer may have same count as one relative.

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The SF12-questionnaire (Physical Health Component Scale [PCS] and Mental Health Component Scale [MCS]) was used to assess quality-of-life (15,16). A very short version of the Health-Anxiety Inventory (HAI) (17) was used to measure health anxiety. The impact of genetic test result disclosure was assessed with the distress, uncertainty, and positive-experience scales of the Multidimensional Impact of Cancer Risk Assessment (MICRA) questionnaire.(18) Data were collected at baseline (precounseling), immediately postcounseling (post–decision making), and at seven days and, three months after getting the test result. Further follow up at one, two, and three years is in progress. Details are accessible at: http://www.controlled-trials.com/ISRCTN73338115. FH-negative FH-arm participants who completed the study were offered testing at the end of three-years of follow-up.

Trial Management

A customized (prototype-based [19,20]) trial management system was developed for running/managing the study. This included an automated randomization function for group allocation, access to pedigree data, volunteer flagging/tracking, electronic data upload/access, and upgrade capability for protocol development.

Statistical Analysis

Random assignment of 1034 volunteers was completed in July 2010. The primary comparison is based on an intention-to-treat analysis between the PS and FH arms. Baseline characteristics were calculated using descriptive statistics.

The questionnaire data were collected over three time points, and so to adequately deal with clustered data (within individuals over time) a random-effects model (random intercept only) with robust standard errors was used to evaluate the effect of the intervention (genetic testing) on outcome variables. The model included a group effect, time effect, and group-by-time interaction. The group-by-time interaction indicates whether there is a difference in change over time between groups and represents the effect of intervention. Appropriate model-based tests/contrasts were used to investigate group and time differences. Contrast tests were used to compare difference between the groups over time points, specifically between time point 1 vs time point 2 and between time point 1 vs time point 3, as well as an overall time effect between groups (contrast of all three time points), tested on two degrees of freedom. Additional covariables of interest were also included in the model: sex, age, FH, income, and marital status. Predicted mean scale scores with 95% confidence intervals over all values of group and time were plotted, with other covariables set to their mean value.

Statistical analyses used Stata-11.0 (Stata-Corp LP, TX) and R (R-Project GNU General-Public-License, Austria, www.R-project.org) (21). Two-sided *P* values are reported for all statistical tests.

GCaPPS Phase 1 was powered to assess psychological outcomes. A sample size of 509/arm had 90% power to detect a difference of 1.2 points in total HADS scores between the two groups assuming a common SD of 5.9 and $\alpha = 0.05$.

Results

Between August 2008 and July 2010, 1615 people registered and 1168 attended genetic counseling. Of these, eight (0.7%) were excluded: six FDR of BRCA carriers, two with fewer than four AJ grandparents. A total of 1042 (89%) consented to genetic testing, of whom eight withdrew within three weeks, and 1034 (691 women, 343 men) were randomly assigned to the PS (n = 530) or FH (n = 504) arms (Figure 1). Reasons for withdrawal (n = 17) included: death (n = 2), death of spouse (n = 1), relocation (n = 1), changed mind (n = 4), not wishing to fill more questionnaires/continue (n = 4), results no longer felt relevant (n = 2), and none given (n = 3). A total of 1017 were eligible for analysis.

FH and PS groups were comparable at baseline (Table 2). The mean age of participants was 54.3 (SD = 14.66) years; 33.2% were men, and 66.8% women. Thirteen (7BRCA1, 6BRCA2) carriers were detected in the PS arm (prevalence = 2.45%, 95% confidence interval [CI] = 1.31 to 4.16). Of these, only three had a clinically significant FH (FH-positive), indicating that 10/13 (77%) carriers in the PS arm would not have been detected by FH alone. Nine carriers (five BRCA1, four BRCA2) were detected in the FH arm (prevalence = 1.79%, 95% CI = 0.82% to 3.36%) (group difference: P = .522). Five more carriers were detected among FH-negative FH-arm participants following study completion.

The group-by-time interaction effect in the random effects model was not statistically significant for outcomes of anxiety, depression, quality-of-life, health anxiety, distress, and uncertainty associated with genetic testing (Tables 3 and 4). This indicates that there is no evidence that population-based genetic testing has different psychological or quality-of-life effects than an FH-based approach over time. The group-by-time interaction for positive experience was of borderline statistical significance (*P* = .04), with scores being higher in the population-screening arm and for men (Table 4). Modeling showed lower levels of anxiety and health anxiety in participants who were older (*P* = .002) and with higher income (*P* < .0005) and in men compared with women (*P* < .0005) (Tables 3 and 4). Depression was also lower in higher income participants (*P* < .0005) (Table 4). Being married and having higher incomes were associated with statistically significantly lower levels of distress and uncertainty following genetic testing, but this was not affected by sex, age, or FH (Table 4).

Contrast tests indicated an overall decrease in anxiety (*P* = .0001), distress (*P* = .04), and uncertainty (*P* = .005) with time. The majority of decline in anxiety was observed in the baseline to seven days (-0.64) period, rather than the seven days to three months (-0.24) period. Positive-experience scores increased (*P* = .0001), but quality-of-life and health anxiety did not change with time. Predicted mean plots (Supplementary Figures 1–9, available online) illustrate these effects. The mean HADS, SF12, HAI, and MICRA scores at seven days/three months are given in Table 5.

The overall BRCA1/2 prevalence detected was 2.45% (95% CI = 1.31% to 4.16%). Of the 1034 participants 128 (12.4%, 95% CI = 10.4% to 14.5%) were FH positive. In our sample, the population prevalence of FH-positive BRCA carriers (12/1034) was 1.16% (95% CI = 0.60% to 2.02%) and the population prevalence of BRCA carriers not fulfilling FH-based criteria for testing (FH-negative, 10/530) was 1.89% (95% CI = 0.91% to 3.44%). To date, 210 of the 438 FH-negative participants in the FH arm have completed three years of follow-up and subsequently opted for genetic testing. Five additional BRCA carriers (two BRCA1, three BRCA2) have been detected in these 210 participants, giving a total BRCA prevalence of 15 of 740 or 2.03% (95% CI = 1.14% to 3.32%) in FH-negative individuals. This indicates that a minimum of 15 of 27 (56%) carriers in this population are not detectable by the conventional FH approach, and this figure will rise when the remaining 218 FH-negative participants reach three-year follow-up and are tested. The minimum proportion of carriers detectable by PS in the overall study population was therefore 27 of 1034

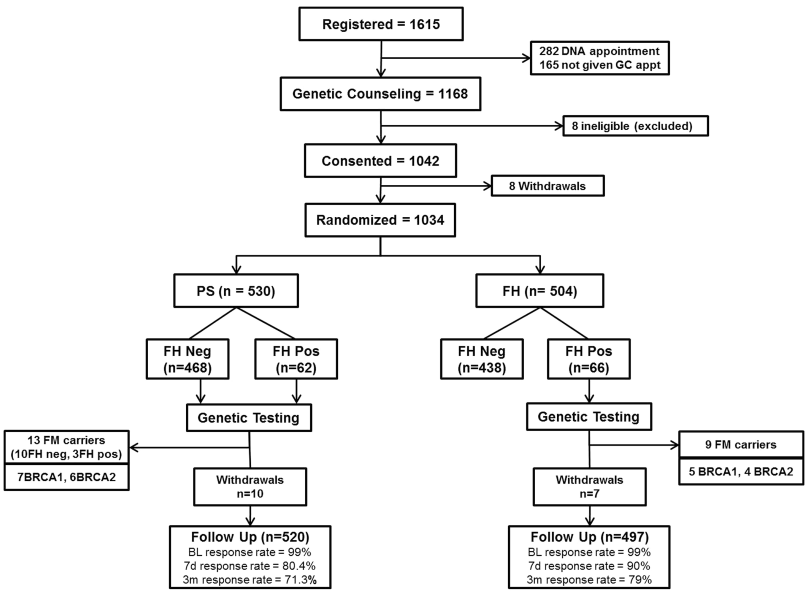

Figure 1. Consort flow chart for the study. BL = baseline; DNA = did not attend; FH = family history; FM = founder mutations; GC = genetic counseling; Neg = negative; Pos = positive; PS = population screening.

Table 2. Baseline characteristics of population screening and family history arms

Characteristic	FH (n = 504)	PS (n = 530)
Age		
Mean age, y (SD)	54.30 (14.31)	54.30 (14.99)
Marital status		
Single, %	9.4	9.0
Married, %	75.5	75.5
Cohabiting (living with partner), %	4.0	4.4
Divorced/separated, %	5.6	6.1
Widowed, %	5.4	5.0
Children		
Have children, %	81.2	82.4
Number of children (SD)	2.3 (1.28)	2.27 (1.3)
Sex		
Men, %	32.1	34.2
Women, %	67.9	65.8
Education		
No formal qualification, %	6.8	7.6
GCSE, O-level, CSE, %	20.7	17.4
NVQ1, NVQ2, %	1.2	1.4
A-level, NVQ-3, %	10.2	11.8
NVQ-4, %	2.5	1.2
Bachelors, %	37.1	40.7
Masters, %	16.8	15.6
PhD, %	4.7	4.4
Income, £		
<10 000, %	4.3	5.1
10 000–19 900, %	7.2	8.5
20 000–29 900, %	9.7	9.6
30 000–39 900, %	12.7	13.0
40 000–49 900, %	12.9	10.9
≥50 000, %	53.2	52.9
Affiliation/identity		
Unaffiliated, %	15.6	14.0
Liberal, %	10.2	8.2
Reform, %	16.0	15.1
Traditional, %	25.5	24.9
Conservative/Masorti, %	10.0	8.2
Orthodox, %	22.6	29.5
FH		
FH positive (AJ criteria), %*	13.1	11.7
FH		
FH positive (extended non-AJ criteria), %†	3.2	3.0
Psychiatric history		
h/o depression, %	12.9	12.9
h/o any psychiatric illness, %	5.7	4.3
h/o medication for psychiatric condition, %	17.0	14.4
Current medication for psychiatric condition, %	4.9	6.4

* Ashkenazi Jewish criteria: high-risk Ashkenazi Jewish criteria (used for randomization), Table 1. AJ = Ashkenazi Jewish; h/o = history of; FH = family history; NVQ = National Vocational Qualification; PS = population screening; SD = standard deviation.

† Non-AJ criteria: extended high-risk criteria for the general population (see Table 1).

(prevalence = 2.61%, 95% CI = 1.73% to 3.78%). For 27 BRCA carriers in the population, the sensitivity of an FH-based approach is 44.4% (95% CI = 26.4 to 63.9%), while the positive (PLR)- and negative-likelihood ratios (NLR) are 3.86 (95% CI = 2.2 to 5.81) and 0.63 (95% CI = 0.41 to 0.84), respectively. FH details of BRCA carriers are given in Supplementary Table 1 (available online).

Discussion

To the best of our knowledge, this is the first population-based RCT without ascertainment biased by cancer history in self/family, comparing FH and population-based approaches for testing dominant-gene disorders. While previous single-arm studies have suggested that population testing could detect more carriers than FH-based testing, they were not designed to or able to compare the psychological/quality-of-life implications of population-based testing with the current standard of care. Our finding of no statistically significant short-term differences between FH and population-based approaches with respect to levels of anxiety, depression, health anxiety, physical/mental well-being, distress, and uncertainty linked to genetic testing is reassuring. It confirms that population-based genetic testing in the majority of people does not harm quality-of-life or psychological well-being, or lead to excessive health concerns, and is similar to findings among individuals being tested using current clinical criteria (8,13,22).

That participation in the program was associated with decreases in anxiety and uncertainty linked to genetic testing is heartening. This is consistent with many earlier reports that identified important psychological benefits of testing (8,13,22,23), though a few reports have found increased distress (24). A population-based single-arm study in unselected Canadian Jewish women undertaken around the same time as our study reported increased levels of cancer-related distress at one year in founder mutation–positive but not founder mutation–negative women. However, this was not an RCT and did not compare the FH and population-screening approaches to genetic testing. In addition, none of the women received pretest genetic counselling, though 93% expressed satisfaction with the testing process (25). Data on long-term outcomes from GCaPPS participants are still being collected and will be reported in due course.

This is the first report on factors affecting psychological health and quality-of-life following genetic testing for cancer-predisposing genes in an unselected population of men and women. FH did not affect levels of general anxiety, health anxiety, depression, quality-of-life, or distress/uncertainty/experience specific to genetic testing (Tables 3 and 4). This finding is consistent with an earlier study (26) but contrary to another small study (27) reporting higher cancer-specific distress at six months in increased-risk compared with average-risk participants. In the latter, absolute levels of stress were not high and overall stress decreased with time (27). Support provided by a spouse and higher income had a beneficial impact on anxiety and uncertainty. Our findings are largely in agreement with normative data from other populations (28–30), while few of the variations observed may reflect population-based differences in the Ashkenazi UK community. It is important to note that though the effects of a number of demographic variables on outcomes observed are statistically significant, they may reflect a large sample size. Given the modest absolute effect sizes, most are unlikely to be clinically relevant.

The decrease in uncertainty (MICRA [18]) specifically associated with genetic testing and the lack of difference between PS and FH groups reconfirms that testing in a low-risk population has similar benefits to testing of a high-risk population. The positive-experience scale is reverse scored and increase in scores with time may be related to the possibility of reducing family support or relief with the passage of time following receipt of test result. This increase was statistically significantly greater for men than women ($P < .0005$) and in those in the population-screening arm, but not affected by age or FH. These data suggest that men and women may respond differently to the experience

Table 3. Random effect models for difference in psychological and quality-of-life outcomes between FH and PS groups over time

Model and variable	Coef.	Std. Err	P>|z|	95% CI
Random effects model for HADS				
Group	−0.472	0.344	0.169	−1.146 to 0.201
Occasion 2	−0.473	0.484	0.328	−1.422 to 0.475
Occasion 3	−0.881	0.740	0.234	−2.331 to 0.570
Group#Occasion				
1 2	−0.473	0.484	0.328	−1.422 to 0.475
1 3	−0.881	0.740	0.234	−2.331 to 0.570
Sex	−1.292	0.360	<0.0005	−1.997 to −0.587
FH	0.651	0.506	0.198	−0.341 to 1.643
Age	−0.035	0.011	0.002	−0.057 to −0.013
Income	−0.544	0.128	<0.0005	−0.795 to −0.293
Marital status	0.556	0.460	0.227	−0.345 to 1.458
HADS depression				
Group	−0.220	0.166	0.184	−0.545 to 0.105
Occasion 2	0.114	0.309	0.711	−0.491 to 0.719
Occasion 3	−0.141	0.392	0.718	−0.910 to 0.627
Group#Occasion				
1 2	−0.330	0.323	0.307	−0.962 to 0.303
1 3	−0.108	0.405	0.790	−0.901 to 0.685
Sex	−0.166	0.173	0.337	−0.505 to 0.173
FH	0.345	0.253	0.173	−0.151 to 0.840
Age	−0.002	0.005	0.710	−0.012 to 0.008
Income	−0.254	0.064	<0.0005	−0.379 to −0.129
Marital status	0.267	0.223	0.232	−0.171 to 0.705
HADS anxiety				
Group	−0.252	0.228	0.270	−0.699 to 0.196
Occasion 2	−0.584	0.325	0.072	−1.220 to 0.0526
Occasion 3	−0.738	0.434	0.089	−1.589 to 0.113
Group#Occasion				
1 2	−0.126	0.350	0.719	−0.811 to 0.560
1 3	−0.315	0.457	0.491	−1.210 to 0.580
Sex	−1.129	0.231	<0.0005	−1.582 to −0.676
FH	0.305	0.334	0.361	−0.349 to 0.959
Age	−0.033	0.008	<0.0005	−0.048 to −0.018
Income	−0.288	0.081	<0.0005	−0.447 to −0.130
Marital status	0.285	0.293	0.331	−0.289 to 0.860
Random effects model for SF12				
SF12-MCS				
Group	0.373	0.356	0.295	−0.325 to 1.071
Occasion 2	0.493	0.734	0.502	−0.945 to 1.932
Occasion 3	−0.289	0.690	0.676	−1.641 to 1.064
Group#Occasion				
1 2	−0.647	0.784	0.409	−2.183 to 0.889
1 3	−0.058	0.734	0.937	−1.496 to 1.381
Sex	0.480	0.325	0.141	−0.158 to 1.117
FH	−1.007	0.531	0.058	−2.047 to 0.033
Age	0.081	0.011	0.000	0.059 to 0.102
Income	0.084	0.120	0.481	−0.151 to 0.319
Marital status	0.994	0.453	0.028	0.106 to 1.882
SF12-PCS				
Group	0.193	0.330	0.558	−0.453 to 0.839
Occasion 2	0.634	0.625	0.311	−0.592 to 1.859
Occasion 3	0.619	0.606	0.307	−0.568 to 1.807
Group#Occasion				
1 2	−0.797	0.669	0.233	−2.108 to 0.514
1 3	−0.877	0.651	0.178	−2.154 to 0.399
Sex	1.656	0.301	<0.0005	1.066 to 2.246
FH	0.344	0.465	0.460	−0.568 to 1.256
Age	−0.092	0.011	<0.0005	−0.115 to −0.070
Income	0.361	0.113	0.001	0.139 to 0.583
Marital status	0.080	0.415	0.846	−0.733 to 0.894

The group-by-time interaction was not statistically significant for any of the models. Reference categories for the following variables is denoted by*: *Group 0 = FH (family history); Group 1 = PS (population screening); *Occasion 1 = baseline; Occasion 2 = time point 2 (7 days post test result); Occasion 3 = time point 3 (three months post test result); Sex 0 = female; Sex 1 = male; *FH 0 = low risk; FH 1 = high risk. *Marital Status 0 = live alone, ie, single/divorced/widowed; marital Status 1 = live with partner, ie, married/cohabiting. Income as "continuous variable," but measured in £10 000 increments. Age in years (continuous variable). Coef = coefficient; Err = error; FH = family history; Group#Occasion = group-by-time interaction effect; HADS = Hospital Anxiety and Depression Scale; PS = population screening; SF12 PCS = SF12 quality-of-life physical component scale; SF12 MCS = SF12 quality-of-life mental component scale; QoL = quality-of-life; Std = standard.

Table 4. Random effects models for health anxiety, distress, uncertainty, and positive experience outcomes*

Model and variable	Coef.	Std. Err	z	P>|z|	95% CI
Random effects model for HAI					
Group	−0.088	0.171	−0.510	0.609	−0.423 to 0.248
Occasion_2	0.167	0.279	0.600	0.549	−0.380 to 0.715
Occasion_3	−0.037	0.360	−0.100	0.918	−0.743 to 0.669
Group#Occasion†					
1 2	0.019	0.295	0.060	0.949	−0.561 to 0.598
1 3	0.090	0.372	0.240	0.810	−0.641 to 0.820
Sex	−0.486	0.165	−2.950	0.003	−0.809 to −0.163
FH	0.097	0.271	0.360	0.721	−0.434 to 0.629
Age	−0.011	0.006	−2.040	0.042	−0.023 to −0.0004
Marital status	0.245	0.213	1.150	0.251	−0.173 to 0.663
Income	−0.153	0.061	−2.500	0.012	−0.272 to −0.033
Random effects model for MICRA					
MICRA distress					
Group	−0.790	0.853	−0.930	0.354	−2.461 to 0.881
Occasion_3	−1.159	0.682	−1.700	0.089	−2.495 to 0.177
Group#Occasion‡					
1 3	0.945	0.691	1.370	0.172	−0.410 to 2.301
Sex	−0.010	0.205	−0.050	0.962	−0.411 to 0.392
FH	0.537	0.494	1.090	0.278	−0.432 to 1.506
Age	−0.009	0.010	−0.890	0.376	−0.028 to 0.10
Marital status	0.331	0.113	2.91	0.004	0.108 to 0.553
Income	−0.216	0.109	−1.98	0.047	−0.430 to −0.002
MICRA Uncertainty					
Group	0.062	1.127	0.060	0.956	−2.148 to 2.272
Occasion_3	−0.474	0.651	−0.730	0.466	−1.750 to 0.802
Group#Occasion‡					
1 3	−0.133	0.680	−0.200	0.845	−1.466 to 1.199
Sex	−0.389	0.398	−0.980	0.328	−1.169 to 0.391
FH	1.359	0.762	1.780	0.075	−0.135 to 2.853
Age	0.003	0.017	0.210	0.836	−0.029 to 0.036
Marital status	0.635	0.225	2.83	0.005	0.195 to 1.076
Income	−0.418	0.18	−2.32	0.02	−0.771 to −0.065
MICRA positive Experience					
Group	−1.509	1.078	−1.400	0.162	−3.622 to 0.604
Occasion_3	0.915	0.936	0.980	0.328	−0.919 to 2.749
Group#Occasion‡					
1 3	2.078	1.010	2.060	0.040	0.097 to 4.059
Sex	3.370	0.607	5.550	<0.0005	2.18 to 4.56
FH	−0.746	0.738	−1.010	0.312	−2.193 to 0.700
Age	−0.019	0.021	−0.900	0.369	−0.062 to 0.023
Marital status	−0.297	0.317	−0.94	0.349	−0.918 to 0.325
Income	−0.016	0.177	−0.09	0.927	−0.364 to 0.331

The group-by-time interaction was not significant for the Health Anxiety Inventory scale, the Multidimensional Impact of Cancer Risk Assessment scale (MICRA)–distress or MICRA-uncertainty models, but was of borderline significance for the MICRA-positive experience model. Reference categories for the following variables is denoted by*: *Group 0 = FH (family history); Group 1 = PS (population screening); Occasion 1 = baseline; Occasion 2 = time point 2 (7 days post test result); Occasion 3 = time point 3 (three months post test result); Sex 0 = female; Sex 1 = male; FH 0 = low risk; FH 1 = high risk; Marital Status 0 = live alone, ie, single/divorced/widowed; Marital Status 1 = live with partner, ie, married/cohabiting; Income as "continuous variable," but measured in £10 000 increments; Age in years (continuous variable). Coef = coefficient; Err = error; FH = family history; Group#Occasion = group-by-time interaction effect; HAI = Health Anxiety Inventory Scale; MICRA = Multidimensional Impact of Cancer Risk Assessment Scale; PS = population screening; REM = random effects model; Std = standard.

† Occasion 1 is the reference variable for HAI random effects model.

‡ Occasion 2 is the reference for MICRA random effects model.

of receiving genetic test results. It is possible that women and those with a strong FH feel more supported/relieved. This finding has not been reported before in a population-based setting. While the scores are useful for monitoring, the thresholds of clinical significance are unknown. The interpretation of these findings is limited by the MICRA development methodology, which was based solely on a high-risk population that lacked men. Further research into developing and validating instruments specific to genetic testing in low-risk populations is warranted.

At least 56% of carriers in our study population would not have been detected using traditional clinical criteria. This is also the first study to report and confirm that the UK prevalence of Jewish BRCA founder mutations is similar to findings from other regions (10,31). Our prevalence estimates for FH-positive (1.16%) and FH-negative (1.89%) carriers suggest that the proportion of undetectable carriers in the entire study population using FH alone could reach 63%. This finding is consistent with an initial Washington (10) study and with Canadian (32) and Israeli (33) single-arm studies undertaken around the time of this trial, in

Table 5. Mean HADS, SF12, HAI, and MICRA scores at baseline, 7 days and 3 months follow up by group*

Mean score	FH (n = 504)	PS (n = 530)
HADS		
HADS total BL (SD)	9.1 (5.3)	8.8 (5.25)
HADS total 7 d (SD)	9.64 (5.04)	7.59 (5.15)
HADS total 3 mo (SD)	9.12 (6.16)	7.3 (5.23)
HADS anxiety BL (SD)	6.16 (3.46)	6.01 (3.61)
HADS anxiety 7 d (SD)	6.04 (3.4)	5.16 (3.42)
HADS anxiety 3 mo (SD)	5.9 (3.72)	4.8 (3.38)
HADS depression BL (SD)	2.94 (2.55)	2.78 (2.45)
HADS depression 7 d (SD)	3.61 (2.76)	2.44 (2.48)
HADS depression 3 mo (SD)	3.22 (3.01)	2.5 (2.55)
SF12 QoL		
SF12 physical scale BL (SD)	49.17 (5.15)	49.22 (5.08)
SF12 physical scale 7 d (SD)	49.13 (5.13)	49.01 (5.11)
SF12 physical scale 3 mo (SD)	48.88 (5.41)	48.83 (5.46)
SF12 mental scale BL (SD)	52.14 (5.44)	52.28 (5.49)
SF12 mental scale 7 d (SD)	52.42 (5.28)	52.55 (5.10)
SF12 mental scale 3 mo (SD)	52.16 (5.08)	52.34 (4.95)
vsHAI		
vsHAI score BL (SD)	3.1 (2.63)	3.08 (2.51)
vsHAI score 7 d (SD)	3.45 (2.72)	3.18 (2.6)
vsHAI score 3 mo (SD)	3.71 (2.61)	2.99 (2.47)
MICRA		
MICRA distress score 7 d (SD)	1.8 (4.43)	0.78 (2.7)
MICRA uncertainty score 7 d (SD)	4.4 (5.97)	2.98 (4.78)
MICRA positive experiences score 7 d (SD)	6.25 (5.49)	6.13 (6.03)
MICRA distress score 3 mo (SD)	1.04 (2.08)	0.59 (2.28)
MICRA uncertainty score 3 mo (SD)	3.71 (4.94)	2.22 (4.39)
MICRA positive experiences score 3 mo (SD)	7.42 (6.81)	9.06 (7.2)

* BL = baseline; FH = family history; HADS = Hospital Anxiety and Depression Scale; HAI = Health Anxiety Inventory; MICRA = Multidimensional Impact of Cancer Risk Assessment Scale; PS = population screening; SD = standard deviation; SF12 QoL = SF12 quality-of-life scale.

which 40% (10), 55% (32), and 63% (33) of carriers, respectively, lacked a strong FH of cancer. It corroborates data on limited family structure (34) and reports from cancer case series unselected for FH, where 50% to 75% of carriers lacked a clinically significant FH (11,12,35–38). We estimate that many more carriers could be detected using a PS approach than by conventional FH-based testing (2.61% vs 1.16%). Taken together, these data clearly illustrate the limitations of the current UK threshold for BRCA1/2 genetic testing. Lack of FH may be because of limited communication, lack of awareness, inaccuracies in FH, family lost in the Holocaust, family migration, small family size, paternal transmission, male preponderance, few women inheriting the mutation, and chance.

If the current UK threshold for FH-based testing were relaxed to include a BRCA-related cancer (breast/ovary/prostate) in an FDR under age 60 years, an FDR at any age, a second-degree relative (SDR) under age 60 years or an SDR at any age, then, correspondingly, a further two, four, or five founder mutation carriers, respectively, would be reclassified as FH positive and detected from amongst the current 15 FH-negative volunteers (Supplementary Table 1, available online). However, this increase in sensitivity from 44.4% to 62.9% would be at the cost of a decrease in specificity and a much lower threshold of BRCA probability for testing.

The difference in number of FH-positive carriers between the FH (9/66) and PS (3/62) arms is likely to be explained by the small sample size and chance. The high population prevalence of carriers without a strong FH (1.89%) reveals a substantial at-risk population not detectable using currently available models/FH-based criteria. It suggests that a population-based approach to genetic-testing requires careful consideration. Validation studies in high-risk populations show that BRCA risk prediction models are moderately effective in identifying carriers (area under the curve [AUC] = 0.67–0.8), are poor at ruling out the presence of a mutation (39), underestimate the probability of detecting mutations at low (≤10%), and intermediate (10%–40%) probability levels, and overestimate mutations at high-probability thresholds (40–42). Our findings of a PLR equalling 3.8 and an NLR equalling 0.63 reconfirm the poor ability of FH to detect BRCA carriers or rule out the presence of a mutation in a population-based cohort. Should the number of carriers be greater than 27, the PLR would be even lower and the NLR even higher. For comparison, the PLR/NLR for mammography is 9.4/0.19 (43).

Three hundred and twelve BRCA carriers (51% via predictive testing, 49% new mutations) were detected from 2000 to 2010 through London NHS laboratories using FH-based criteria. The total estimated London AJ BRCA carriers eligible for testing (2.45% of 105 600 estimated AJ population >18 years) is 2587. Over a period of 10 years, only 12% of these have been identified. Although this figure excludes some private sector testing, most genetic testing in the UK is undertaken within the NHS. Given the options that now exist for cancer risk management and prevention, this raises questions about the current FH-based approach for identifying people at risk and makes it imperative to explore new approaches for risk prediction. The optimal approach adopted will also need to take into account the cost of case identification.

There is reasonable acceptability of BRCA testing among interested community members. Almost three-quarters (72%) of those expressing an interest attended counseling, and the majority (89%) consented to testing. Our study has several advantages, including the randomized design, high questionnaire response rates, and pretest genetic counseling received by participants. We successfully provided counseling within a novel community and high street–based setting, away from the traditional hospital base. Recently reported population studies were single arm and offered counseling only post-testing (32,33). Both men and women participated in GCaPPS, and the results give an initial estimate of the distribution of people who may come forward should BRCA testing be offered on a population basis. In keeping with this, the prevalence of psychiatric morbidity (44), levels of anxiety, depression (45), and quality-of-life (28,29) in our cohort (Table 2) are similar to reports from UK population-based surveys (44).

While the initial results from our study are promising, the study is limited by the small number of carriers and the short-term follow-up. Some important questions highlighted above remain to be answered and longer-term follow-up data evaluated before committing substantial resources to population-based genetic testing. We have not had sufficient power to examine differences in psychological impact or behavioral outcomes (uptake of screening/preventive options) between BRCA carriers detected through FH and population-based approaches. These issues will be addressed in the next phase of the trial. Participants in our study had higher income and education levels, but this is consistent with the income/education levels found in the UK Jewish population compared with the general population.

There remains some debate on whether mutations detected in the setting of a family history will have greater risk than those detected in a population without family history. Penetrance

estimates may be upwardly biased for mutation carriers in the presence of residual familial aggregation if the analytic method assumes that disease risk depends on mutation status only. Data from the population-based Washington Ashkenazi Study corrected for ascertainment (46–48), a meta-analysis of population/case-series based data (2), and, more recently, penetrance estimates from a single-arm Israeli study (corrected for previous potential biases of estimates derived mainly from female carriers) (33) indicate that Jewish BRCA1/BRCA2 carriers ascertained on a population basis and those without a strong family history of cancer have high risks for breast/ovarian cancer, though these estimates are clearly lower than estimates obtained from high-risk families/cancer genetic clinics.

The whole issue of cancer risk estimation/penetrance is complex, and current estimates used in clinical practice are derived from models that do not incorporate a number of epidemiologic and/or genetic variables that can modify risk. The complexities and limitations around risk estimation were addressed via individualized pretest genetic counseling undertaken by counselors with considerable experience in cancer risk estimation. While the baseline risk estimates used were based on those corrected for population-based ascertainment, the volunteer's family history was reviewed and taken into account during this process.

New gene sequencing technologies (49) and the falling cost of genetic testing may make it economically feasible to test large populations in the future. However, a number of issues related to sensitivity, specificity, variants of undetermined significance, and non-zero error rate linked to new testing technologies need further clarifying and resolving before such an approach can be assessed in the non-AJ general population. Our study is limited by being specific to the Jewish community and, hence, our findings on uptake, psychological impact, and quality-of-life cannot be directly extrapolated/applied to the general non-AJ population. While applicability of such an approach to the general non-AJ population requires more research, our findings are relevant to and carry an important message for impact of population-based testing in Ashkenazi Jews. The lack of detrimental psychological/quality-of-life outcomes coupled with a health economic benefit found in our decision-analytic model has important policy implications for the AJ population, which can save lives. This will require a change in the current paradigm of an FH-based approach to genetic testing in this population. Efficient, acceptable, and more cost-effective ways of delivering information on genetic risk on a population basis will also be necessary for this and require future research.

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Notes

Ethics approval and trial registration: The Genetic Cancer Prediction through Population Screening study received full ethics approval from the Institute of Child Health/Great Ormond Street Hospital Research Ethics Committee on June 8, 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.

Contribution to authorship: IJ conceived the trial and secured the funding. RM, IJ, and UM were responsible for design of the study and literature review. RM, IJ, UM, JW, KL, SG, SS, and AK were involved in developing interventional questionnaires. RM, KL, and MB were involved in data collection and analysis. RM and MB did the statistical analysis. RM and MB prepared the tables and figures. RM and IJJ prepared the first draft of the manuscript. RM, IJ, UM, KL, JW, SG, LS, NB, RD, AK, HD, YW, CC, IT, AMG, and UB were involved in running the study. YW did the genetic testing. RT and CJ helped with data collection from genetic laboratories. All authors critically contributed to and revised the manuscript and approved the final version.

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