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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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Running Head :

Randomized trial for BRCA testing in Ashkenazi Jews

ABSTRACT

Background: Technological advances raise the possibility of systematic population-based genetic testing for cancer predisposing mutations, but it is uncertain whether benefits outweigh its 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 than18years were recruited by self-referral after pre-test 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: 1168 AJ individuals were counseled, 1042 consented, 1034 were randomized (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, 9 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 7 days or 3 months on measures of anxiety, depression, health anxiety, distress, uncertainty and quality of life. Contrast tests indicated that overall anxiety (p=0.0001), and uncertainty (p=0.0008) associated with genetic testing decreased; positive experience scores increased (p=0.0001); 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 to 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.

INTRODUCTION

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%-80% risk of breast cancer, 20%-45% risk of ovarian cancer (OC) and 5%-25% risk of prostate cancer.[1-5] Established management strategies for high-risk individuals include: (a) risk-reducing salpingo-oophorectomy(RRSO) to prevent tubal/ovarian cancer (HR, 0.21),[6] (which also halves breast cancer risk in pre-menopausal women),[6] (b) risk-reducing mastectomy to prevent breast cancer,[7-9] (c) early onset breast screening (MRI/mammograms) and (d) pre-implantation 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 non-carriers 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 to 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 a 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, 4-AJ grandparents). Exclusion criteria were: known BRCA mutation, first degree relative (FDR) of a BRCA carrier or previous BRCA testing. This article reports on (a) founder-mutations detected, (b)

acceptability of the test, and (c) 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 web-site (www.gcapps.org). Volunteers received structured, non-directive pre-test 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 post-counseling.

Randomization

Consenting participants were randomized post-counseling using a computer generated random-number algorithm. Genetic counselors were blinded to group

allocation during counseling and recruitment. Participants were informed of their randomized 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 a 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 2000-2010.

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 a 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

Socio-demographic and FH data were collected using a customized questionnaire. Depression and anxiety were assessed with the Hospital Anxiety and Depression Scale (HADS).[14] 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 (pre-counseling), immediately post-counseling (post-decision making), and at 7-days and, 3-months after getting the test result. Further follow up at 1, 2 and 3 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 3-years 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

Randomization 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 3 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

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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 versus time point 2 and between time point 1 versus time point 3, as well as an overall time effect between groups (contrast of all 3 time points), tested on 2 degrees of freedom. Additional covariates of interest were also included in the model: sex, age, FH, income and marital status. Predicted mean scale scores with 95% CI over all values of group and time were plotted, with other covariates set to their mean value. Statistical analyses used Stata-11.0 (Stata-Corp LP, Texas, USA) 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 α=0.05.

RESULTS

Between August 2008 and July 2010, 1615 people registered and 1168 attended genetic counseling. Of these, 8 (0.7%) were excluded: six FDR of BRCA carriers, two with <4 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 randomized 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), 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%,CI:1.31,4.16). Of these only 3 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 (5 BRCA1, 4 BRCA2) were detected in the FH arm (prevalence=1.79%, CI:0.82,3.36%) (group difference: $p=0.522$). 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 3,4). This indicates that there is no evidence that population-based genetic testing has different psychological or quality of life effects than a FH-based approach over time. The group-by-time interaction for positive experience was of borderline statistical significance ($p=0.04$), 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 ($p=0.002$) and with higher income ($p<0.0005$) and in men compared to women ($p<0.0005$),(Tables 3,4). Depression was also lower in higher income participants ($p<0.0005$),(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=0.0001), distress (p=0.04), and uncertainty (p=0.005) with time. The majority of decline in anxiety was observed in the baseline-7days (-0.64) rather than the 7days-3months (-0.24) period. Positive-experience scores increased (p=0.0001), but quality-of-life and health-anxiety did not change with time. Predicted mean plots (Supplementary Figures1-9, available online) illustrate these effects. The mean HADS, SF12, HAI and MICRA scores at 7days/3-months are given in Table 5.

The overall BRCA1/2 prevalence detected was 2.45% (95% CI:1.31%,4.16%). Of the 1034 participants 128 (12.4%, CI:10.4,14.5%) were FH positive. In our sample the population prevalence of FH-positive BRCA carriers (12/1034) was 1.16% (CI:0.60%,2.02%) and the population prevalence of BRCA carriers not fulfilling FH-based criteria for testing (FH-negative,10/530) was 1.89% (CI:0.91%,3.44%). To date, 210 of the 438 FH-negative participants in the FH arm have completed 3 years of follow-up and subsequently opted for genetic testing. Five additional BRCA carriers (2 BRCA1, 3 BRCA2) have been detected in these 210 participants, giving a total BRCA prevalence of 15/740 or 2.03% (CI:1.14,3.32%) in FH-negative individuals. This indicates that a minimum of 15/27 (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 3-year follow-up and are tested. The minimum proportion of carriers detectable by PS in the overall study population was therefore 27/1034 (prevalence=2.61%; CI:1.73,3.78%). For 27 BRCA carriers in

the population, the sensitivity of a FH-based approach is 44.4% (95%CI:26.4,63.9%) while the positive-(PLR) and negative-likelihood-ratios (NLR) are 3.86 (95%CI:2.2,5.81) and 0.63 (95%CI:0.41,0.84) respectively. FH details of BRCA carriers are given in Supplementary Table 1.

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 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 a RCT and did not compare the FH and population-screening approaches to genetic testing. In addition none of the women received pre-test genetic-counseling 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 3,4). This finding is consistent with an earlier study [26] but contrary to another small study [27] reporting higher cancer-specific distress at 6-months in increased risk compared to 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 ($p < 0.0005$) 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 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 suggests 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 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%-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 due to 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 a FDR <60 years, a FDR at any age, a second degree relative (SDR) < 60 years or a SDR at any age, then, correspondingly, a further 2, 4, 4 or 5 founder mutation carriers, respectively, would be re-classified as FH positive and detected from amongst the current 15 FH negative volunteers (Supplementary Table 1). However, this increase in sensitivity from 44.4% to 62.9% would be at the cost of 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 (AUC,0.67-0.8), 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 over-estimate mutations at high-probability thresholds [40-42]. Our findings of a PLR=3.8 and an NLR=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 >27, the PLR would be even lower and NLR even higher. For comparison the PLR/NLR for mammography is 9.4/0.19 [43].

312 BRCA carriers (51% via predictive testing, 49% new mutations) were detected from 2000-2010 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 pre-test 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 to 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] meta-analysis of population/case-series based data [2], and, more recently, penetrance estimates from a single arm Israeli study [33] (corrected for previous potential biases of estimates derived mainly from female carriers) 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 which do not incorporate a number of epidemiologic and/or genetic variables which can modify risk. The complexities and limitations around risk estimation were addressed via individualized pre-test 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 a 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.

Notes

Ethics approval and trial registration

The GCaPPS study received full ethics approval from the Institute of Child Health/ Great Ormond Street Hospital Research Ethics Committee on 8th 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.

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, AK were involved in developing interventional questionnaires. RM, KL, MB were involved in data collection and analysis. RM, MB did the statistical analysis. RM, MB prepared the tables and figures. RM, IJJ prepared the first draft of the manuscript. RM, IJ, UM, KL, JW, SG, LS, NB, RD, AK, HD, YW, CC, IT, AMG, 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.

Disclaimers/ Conflict of interest statement

IJ had a consultancy arrangement with Becton Dickinson, in the field of molecular markers for ovarian cancer. 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 and a

Director of Women's Health Specialists Ltd. The other authors declare no conflict of interest.

Role of Funding Source

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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 Male Breast Cancer (MBC) (any age)
6)   Personal history (men) of MBC (any age)
*Equivalence of history of ovarian/ primary peritoneal cancer (PPC)/ fallopian tube cancer (FTC) for HR criteria
Extended High-risk criteria for referral of FM negative volunteers to the regional genetic units
Volunteer should fulfil 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)   One ovarian cancer* **and** 1 breast cancer <50 years who are FDR
3)   One 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 i.e. 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) one ≤30 years **or**
  b) two ≤40 years (and all ≤60 years) **or**
  c) one MBC (≤60 years) and other two ≤50years

Male Breast Cancer (MBC)
9)   Two MBC (≤60 years) in the family and proband is a FDR of one 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/ PPC/ FTC for HR criteria **Cases of b/l breast cancer- each breast cancer may have same count as one relative

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

Table 2. Baseline Characteristics of Population Screening and Family History arms

Characteristic		FH (n=504)	PS (n=530)
Age	Mean Age in years (S.D)	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 (S.D)	2.3 (1.28)	2.27 (1.3)
Gender	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%

AJ- Ashkenazi Jewish; FH- family history; NVQ- National Vocational Qualification;

PS- population screening; S.D- standard deviation; h/o = history of.

*AJ Criteria: High-risk Ashkenazi Jewish criteria (used for Randomization), Table 1

†Non-AJ Criteria: Extended high-risk criteria for the general population, see Table 1

Table 3. Random Effect Models for difference in psychological and quality of life outcomes between FH and PS groups over time

RANDOM EFFECTS MODEL for HADS				
HADS Total	**Coef.**	**Std. Err**	**P>|z|**	**[95% CI]**
Group	-0.472	0.344	0.169	-1.146, 0.201
Occasion 2	-0.473	0.484	0.328	-1.422, 0.475
Occasion 3	-0.881	0.740	0.234	-2.331, 0.570
Group#Occasion				
1 2	-0.473	0.484	0.328	-1.422, 0.475
1 3	-0.881	0.740	0.234	-2.331, 0.570
Sex	-1.292	0.360	<0.0005	-1.997, -0.587
FH	0.651	0.506	0.198	-0.341, 1.643
Age	-0.035	0.011	0.002	-0.057, -0.013
Income	-0.544	0.128	<0.0005	-0.795, -0.293
Marital Status	0.556	0.460	0.227	-0.345, 1.458
HADS Depression	**Coef.**	**Std. Err**	**P>|z|**	**[95% CI]**
Group	-0.220	0.166	0.184	-0.545, 0.105
Occasion 2	0.114	0.309	0.711	-0.491, 0.719
Occasion 3	-0.141	0.392	0.718	-0.910, 0.627
Group#Occasion				
1 2	-0.330	0.323	0.307	-0.962, 0.303
1 3	-0.108	0.405	0.790	-0.901, 0.685
Sex	-0.166	0.173	0.337	-0.505, 0.173
FH	0.345	0.253	0.173	-0.151, 0.840
Age	-0.002	0.005	0.710	-0.012, 0.008
Income	-0.254	0.064	<0.0005	-0.379 -0.129
Marital Status	0.267	0.223	0.232	-0.171, 0.705
HADS Anxiety	**Coef.**	**Std. Err**	**P>|z|**	**[95% CI]**
Group	-0.252	0.228	0.270	-0.699, 0.196
Occasion 2	-0.584	0.325	0.072	-1.220, 0.0526
Occasion 3	-0.738	0.434	0.089	-1.589, 0.113
Group#Occasion				
1 2	-0.126	0.350	0.719	-0.811, 0.560
1 3	-0.315	0.457	0.491	-1.210, 0.580
Sex	-1.129	0.231	<0.0005	-1.582, -0.676
FH	0.305	0.334	0.361	-0.349, 0.959
Age	-0.033	0.008	<0.0005	-0.048, -0.018
Income	-0.288	0.081	<0.0005	-0.447, -0.130
Marital Status	0.285	0.293	0.331	-0.289, 0.860
RANDOM EFFECTS MODEL for SF12				
SF12- MCS	**Coef.**	**Std. Err**	**P>|z|**	**[95% CI]**

	Coef.	Std. Err	P>|z|	[95% CI]
Group	0.373	0.356	0.295	-0.325, 1.071
Occasion 2	0.493	0.734	0.502	-0.945, 1.932
Occasion 3	-0.289	0.690	0.676	-1.641, 1.064
Group#Occasion				
1 2	-0.647	0.784	0.409	-2.183, 0.889
1 3	-0.058	0.734	0.937	-1.496, 1.381
Sex	0.480	0.325	0.141	-0.158, 1.117
FH	-1.007	0.531	0.058	-2.047, 0.033
Age	0.081	0.011	0.000	0.059, 0.102
Income	0.084	0.120	0.481	-0.151, 0.319
Marital Status	0.994	0.453	0.028	0.106, 1.882
SF12- PCS	**Coef.**	**Std. Err**	**P>|z|**	**[95% CI]**
Group	0.193	0.330	0.558	-0.453, 0.839
Occasion 2	0.634	0.625	0.311	-0.592, 1.859
Occasion 3	0.619	0.606	0.307	-0.568, 1.807
Group#Occasion				
1 2	-0.797	0.669	0.233	-2.108, 0.514
1 3	-0.877	0.651	0.178	-2.154, 0.399
Sex	1.656	0.301	<0.0005	1.066, 2.246
FH	0.344	0.465	0.460	-0.568, 1.256
Age	-0.092	0.011	<0.0005	-0.115, -0.070
Income	0.361	0.113	0.001	0.139, 0.583
Marital Status	0.080	0.415	0.846	-0.733, 0.894

The group-by-time interaction was not statistically significant for any of the models

Coef: coefficient; Err: Error; FH: family history; 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

Group#Occasion- Group-by-time interaction effect

Reference category for variables is denoted by *

*Group 0=FH (family history); Group 1=PS (population screening); *Occasion 1=baseline; Occasion 2= Time point 2 (7days post test result); Occasion 3= Time point 3 (3 months post test result); *Sex 0=female; Sex 1=male; *FH 0=low risk; FH 1=high risk;

*Marital Status 0=live alone i.e single/divorced/widowed; Marital Status 1=live with partner i.e married/cohabiting

Income- as 'continuous variable', but measured in £10,000 increments

Age – in years (continuous variable)

Table 4: Random Effects Models for health anxiety (HAI), distress, uncertainty and positive experience (MICRA) outcomes

RANDOM EFFECTS MODEL for HAI					
HAI	**Coef.**	**Std. Err**	**z**	**P>|z|**	**[95% CI]**
Group	-0.088	0.171	-0.510	0.609	-0.423, 0.248
Occasion_2	0.167	0.279	0.600	0.549	-0.380, 0.715
Occasion_3	-0.037	0.360	-0.100	0.918	-0.743, 0.669
Group#Occasion†					
1 2	0.019	0.295	0.060	0.949	-0.561, 0.598
1 3	0.090	0.372	0.240	0.810	-0.641, 0.820
Sex	-0.486	0.165	-2.950	0.003	-0.809, -0.163
FH	0.097	0.271	0.360	0.721	-0.434, 0.629
Age	-0.011	0.006	-2.040	0.042	-0.023, -0.0004
Marital Status	0.245	0.213	1.150	0.251	-0.173, 0.663
Income	-0.153	0.061	-2.500	0.012	-0.272, -0.033
RANDOM EFFECTS MODEL for MICRA					
MICRA Distress	**Coef.**	**Std. Err**	**z**	**P>|z|**	**[95% CI]**
Group	-0.790	0.853	-0.930	0.354	-2.461, 0.881
Occasion_3	-1.159	0.682	-1.700	0.089	-2.495, 0.177
Group#Occasion‡					
1 3	0.945	0.691	1.370	0.172	-0.410, 2.301
Sex	-0.010	0.205	-0.050	0.962	-0.411, 0.392
FH	0.537	0.494	1.090	0.278	-0.432, 1.506
Age	-0.009	0.010	-0.890	0.376	-0.028, 0.10
Marital Status	0.331	0.113	2.91	0.004	0.108, 0.553
Income	-0.216	0.109	-1.98	0.047	-0.430, -0.002
MICRA Uncertainty	**Coef.**	**Std. Err**	**z**	**P>|z|**	**[95% CI]**
Group	0.062	1.127	0.060	0.956	-2.148, 2.272
Occasion_3	-0.474	0.651	-0.730	0.466	-1.750, 0.802
Group#Occasion‡					
1 3	-0.133	0.680	-0.200	0.845	-1.466, 1.199
Sex	-0.389	0.398	-0.980	0.328	-1.169, 0.391
FH	1.359	0.762	1.780	0.075	-0.135, 2.853
Age	0.003	0.017	0.210	0.836	-0.029, 0.036
Marital Status	0.635	0.225	2.83	0.005	0.195, 1.076
Income	-0.418	0.18	-2.32	0.02	-0.771, -0.065
MICRA Positive Experience	**Coef.**	**Std. Err**	**z**	**P>|z|**	**[95% CI]**
Group	-1.509	1.078	-1.400	0.162	-3.622, 0.604
Occasion_3	0.915	0.936	0.980	0.328	-0.919, 2.749

Group#Occasion‡					
1 3	2.078	1.010	2.060	0.040	0.097, 4.059
Sex	3.370	0.607	5.550	<0.0005	2.18, 4.56
FH	-0.746	0.738	-1.010	0.312	-2.193, 0.700
Age	-0.019	0.021	-0.900	0.369	-0.062, 0.023
Marital Status	-0.297	0.317	-0.94	0.349	-0.918, 0.325
Income	-0.016	0.177	-0.09	0.927	-0.364, 0.331

The group-by-time interaction was not significant for HAI, MICRA-distress or MICRA-uncertainty models, but was of borderline significance for MICRA-positive experience model

Coef: coefficient; Err: Error; FH: family history; HAI - Health Anxiety Inventory scale; MICRA- Multidimensional Impact of Cancer Risk Assessment scale; PS- population screening; REM- Random Effects Model; Std: standard

Group#Occasion- Group-by-time interaction effect

Reference category for variables is denoted by *

*Group 0=FH (family history); Group 1=PS (population screening); Occasion 1=baseline; Occasion 2= Time point 2 (7days post test result); Occasion 3= Time point 3 (3 months post test result); *Sex 0=female; Sex 1=male; *FH 0=low risk; FH 1=high risk; *Marital Status 0=live alone i.e single/divorced/widowed; Marital Status 1=live with partner i.e married/cohabiting; Income- as 'continuous variable', but measured in £10,000 increments; Age – in years (continuous variable)

†Occasion 1 is the reference variable for HAI random effects model and ‡Occasion 2 is the reference for MICRA random effects model.

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

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

BL- baseline, FH- family history, PS- population screening, S.D – Standard

Deviation, 7d- 7 days, 3mth- 3 months; HADS - Hospital Anxiety and Depression

Scale; HAI - Health Anxiety Inventory; SF12 QoL- SF12 quality-of-life scale; MICRA-

Multidimensional Impact of Cancer Risk Assessment scale

Figure 1- Consort flow chart for the study

BL- baseline; d- days; DNA- did not attend; FH- family history, FM- founder
mutations; GC- genetic counseling; m- months; Neg- negative; PS- population
screening, Pos- positive.

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