Randomised trial of population based BRCA testing in Ashkenazi Jews: Long term outcomes

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ABSTRACT

Background:

Unselected population-based *BRCA*-testing provides the opportunity to apply genomics on a population-scale to maximise primary prevention for breast-&-ovarian cancer. **Objective**

To 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:

(a)Population-Screening (PS); (b)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 North-London AJ population.

Inclusion criteria: AJ-women/men >18-years. 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 (a) all participants in PS-arm; (b) those fulfilling FH/clinical-criteria in FH-arm. Linear-mixed models and appropriate contrast-tests were used to analyse 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 well-being/quality-of-life outcomes at baseline/1-year/2-years/3-years follow-up.

Results:

1034 (women=691/men=343) participants randomized 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 to FH-arm over 3-years. No significant difference was observed between FH/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. 18/30(60%) *BRCA*-carriers identified did not fulfil clinical-criteria for *BRCA*-testing. The total *BRCA*-prevalence= 2.9%(CI:1.97%,4.12%). *BRCA1*-prevalence=1.55%(CI:0.89%,2.5%); *BRCA2*-prevalence=1.35%(CI:0.74%,2.26%).

Conclusion:

Population-based AJ *BRCA*-testing doesn't adversely affect long-term psychological well-being or quality-of-life, decreases anxiety and could identify up-to 150% additional *BRCA*-carriers.

Trial-registry:

ISRCTN-73338115

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Key Words:

BRCA1, BRCA2, genetic testing, population testing, Ashkenazi Jews, psychological, quality of life

Tweetable Abstract:

Population *BRCA* testing in Ashkenazi Jews reduces anxiety & doesn't adversely affect psychological health or quality-of-life.

INTRODUCTION

Traditionally ovarian cancer (OC) and breast cancer (BC) prevention has been targeted at high-risk individuals like *BRCA1/BRCA2*-carriers. *BRCA1/BRCA2*-carriers have a 17-44% OC-risk and 69-72% BC-risk till 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 can opt for a range of options to minimise risk: risk-reducing salpingo-oophorectomy (RRSO) to reduce their OC-risk;[2, 3] MRI/mammography screening, risk-reducing mastectomy (RRM)[4], or chemoprevention with selective estrogen-receptor modulators (SERM) to reduce their BC-risk;[5] as well as pre-implantation genetic diagnosis (PGD).[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 the absence of one.[7] Inadequate public and health-professional awareness, complexity of the current structure/referral-pathways, limited genetic-counselling services, has 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] Short-term increase along-with long-term decrease in distress and uncertainty has 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 randomized-controlled-trial (RCT) directly comparing *BRCA*-testing using FH-based clinical-criteria with Population-Screening (PS) or *BRCA*-testing all-participants irrespective of FH (ISRCTN:73338115). Short-term (3-month) outcomes demonstrated that population-testing (compared to FH-testing) did not adversely affect psychological well-being or quality-of-life, while overall anxiety and uncertainty decreased at 3-months follow-up.[14] However, psycho-social 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:

RCT (ISRCTN73338115), with participants randomly allocated to one of two-arms: population-screening (PS) arm, and family-history (FH)-arm. Inclusion-criteria: age >18-years and AJ-ethnicity. Exclusion-criteria: known *BRCA*-mutation, first-degree-relative (FDR) 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 study web-site. All participants received structured non-directive pre-test genetic-counselling prior to consenting for *BRCA*-testing. Baseline data were collected at initial appointment. Consenting participants were randomized (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 group allocated by post. Randomisation was undertaken three weeks after consent to provide a window period for early withdrawal prior to 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 a NHS clinical-genetics laboratory on all PS-arm volunteers and only FH-arm volunteers fulfilling standard FH-based criteria. These clinical/FH-criteria have been described earlier and are given in Table-S1.[14] *BRCA*-mutation positive (and 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 a 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/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. We report on long-term (up-to 3-years) outcomes on (a)psychological-health, (b)quality-of-life and (c)mutation rate. Customised questionnaires were used to collect socio-demographic and FH data. Validated questionnaires were used to assess psychological and quality-of-life outcomes. Anxiety-&-Depression: Hospital Anxiety-&-Depression Scale (HADS);[22] Quality-of-Life: SF12-questionnaire (Physical-Health Component-scale (PCS) and Mental-Health Component-scale

(MCS));[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 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 subject. Each time-point was included as a fixed-effect and interacted with the group-term ('family-history' or 'population-screening') resulting in all 8 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.

Post-modelling, we considered 2 specific pre-defined contrast tests (each on 3-degrees of freedom). Firstly, 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 secondly, 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 to the FH modality by any outcome measure. Potential group differences over the 4 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 8 group-by-time interactions. These marginal predictions, and their confidence-intervals, were then plotted. Statistical-analyses used Stata-11.0 (Stata-Corp LP, Texas/USA). Two-sided p-values are reported for all statistical tests.

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

Patient & Public Involvement (PPI):

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 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:

1168 volunteers underwent pre-test counselling, of whom 1042(89%) consented to *BRCA*-testing over a two year recruitment period. Eight elected to withdraw from the study within the three weeks window period. 1034 (691 women, 343 men) were randomized to the PS(n=530) or FH(n=504) arms. The consort flow-chart is given in Figure-1. A further 17 participants (PS=10,FH=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 fill 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 family-history of cancer. These baseline characteristics

have been described earlier and are given in Table-S2.[14] The questionnaire response rate was 99% at baseline, 77-80% at 1-year, 71-72% at 2-year, 64-71% at 3-year (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 to FH-arm over 3-years time (Table-2,Figure-2). There was no statistically significant difference in depression-scores between 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, while the total HADS-scores decreased over time in PS-arm alone ($p<0.0005$) (Tables-1,2;Figure-2). There was a small increase in depression scores over time within the FH-testing group ($p=0.035$) but not within PS-group (Table-1,2). 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,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 three 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 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&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, 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, 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 to a 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 to FH-based testing.

Linear-mixed models outputs showing the association of covariates with the different outcomes are given in 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($p<0.005$), uncertainty ($p=0.003$) and higher quality-of-life scores($p<0.005$) with genetic-testing (Table-S3). Overall men (compared to women) had lower levels of anxiety($p<0.0005$), 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($p=0.007$) (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 (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($p<0.0005$) but higher mental quality-of-life scores($p<0.0005$) (Table-S3).

530 participants in the PS-arm and 66 in the FH-arm underwent *BRCA*-testing. Thirteen (*BRCA1:7*,*BRCA2:6*) carriers were detected in the PS-arm, of whom 3 were FH-positive. Nine carriers (5 *BRCA1*, 4 *BRCA2*) were detected in the FH-arm.[14] Following completion of the study 3-year follow-up, all FH-negative volunteers in the FH-arm were offered *BRCA*-testing. At the time of our last report,[14] 228 FH-negative volunteers in the FH-arm had not completed *BRCA*-testing. We identified 3 additional *BRCA*-carriers in 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 8 *BRCA*-carriers in the FH-negative FH-arm sub-group. Hence, the total *BRCA*-prevalence in the cohort is 30/1034 (2.9% 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%(CI:0.89%,2.5%) and for *BRCA2* was 1.35%(CI:0.74%,2.26%). The combined *BRCA*-prevalence in FH-positive individuals from both arms is 9.4% (CI:4.9%,15.8%) and prevalence in FH-negative individuals is 1.99% (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 to *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 Ashkenazi-Jews. 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 to FH-based *BRCA*-testing. While 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 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] is supportive of population-testing and complements the quantitative findings from our 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 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 generalizability 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 test result. The small decrease in quality-of-life scores found with time are consistent with normative data showing decrease in quality-of-life with age[30, 31] and the lack of difference observed between the two *BRCA*-testing approaches is reassuring. The baseline distribution of anxiety, depression[32] and quality-of-life[31, 33] scores in our cohort are similar to 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 prior to *BRCA*-testing (in addition to post-test counselling) and inclusion of both women and men in our study. 20% 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 analysis.[29] 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 prior to undergoing genetic-testing.[11] This affected decision making[11] and remains part of current standard clinical guidelines prior to 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 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 is consistent with the income/education levels found in the UK Jewish-population compared to 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 confidence-intervals of other reports.[40-42] Our finding of high *BRCA*-prevalence in FH-negative individuals and 60% *BRCA*-carriers lacking clinical-criteria for testing is similar to other studies which reported this to range from 40-63%.[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 utilise 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 *apriori* 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 only 3% of general and 11% AJ *BRCA*-carriers have been identified in a 16-million population across Greater-London.[9] It is likely 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 makes population-testing feasible. The rapidly changing genomic landscape, improved genetic understanding of disease and increasing awareness offers a massive opportunity to apply this knowledge and technology on a broad population scale to make an important shift in healthcare towards disease prevention. GLOBOCAN data suggest OC/BC cases 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. While recent data suggest genetic testing for BC/OC gene mutations could be cost-effective in general-population women too,[47] additional research including general-population implementation studies are needed to address knowledge gaps before that step can be considered.

Chronic disease is a major public health burden. CDC reports the top five causes of deaths as: 1)heart-disease 2)cancer 3)lung-disease 4)accidents 5)strokes.[48] 50% adults have ≥1 and 25% adults have ≥2 chronic-health conditions and the latter accounts for >90% Medicare expenditure. In England chronic-conditions account for 50% GP appointments, 64% outpatient-appointments, 70% inpatient-bed days, and 70% of the total health-care 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 doesn't adversely affect long-term psychological well-being or quality-of-life and is associated with decreased anxiety compared to 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.

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Disclosure/ Conflict of Interest Statement:

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 Beckton 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 Israel National Institute for Health Policy Research and honorarium for advisory board membership from Astrazeneca/MSD. RM is supported by an NHS Innovation Accelerator (NIA) Fellowship for population testing. The other authors declare no conflict of interest.

Ethics approval

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.

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Contribution to authorship

Conception: RM, IJ. Design & 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

Data sharing

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

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