

1 **A commentary on population genetic testing for primary prevention: changing landscape and the**
2 **need to change paradigm**

3 *Ranjit Manchanda^{1,2,3}, Faiza Gaba^{1,2}

4 ¹Barts Cancer Institute, Queen Mary University of London, Old Anatomy Building, Charterhouse
5 Square, London, EC1M 6BQ, UK

6 ²Department of Gynaecological Oncology, St Bartholomew's Hospital, London, UK, EC1A 7BE

7 ³MRC Clinical Trials Unit at UCL, Institute of Clinical Trials & Methodology, Faculty of Population
8 Health Sciences, University College London, UK.

9

10

11 ***Corresponding author**

12 Dr Ranjit Manchanda

13 Consultant Gynaecological Oncologist, Clinical Senior Lecturer

14 Barts Cancer Institute, Centre for Experimental Cancer Medicine

15 Charterhouse Square, London EC1M 6BQ

16 Department of Gynaecological Oncology

17 Bartshealth NHS Trust, Royal London Hospital

18 10th Floor, South Block, Whitechapel Road, London E1 1BB,

19 Email- r.manchanda@gmul.ac.uk

20

21 **Shortened title:** population testing commentary

22 **Word count:** 1764

23

24

25 **Background**

26 *BRCA1/BRCA2* genes were discovered in early 1990s and clinical testing for these has been
27 available since the mid-1990s. National Institute of Health and Care Excellence (NICE) and other
28 international guidelines recommend genetic-testing at a ~10% probability threshold of carrying a
29 *BRCA*-mutation. A detailed three generation family-history (FH) of cancer is used within complex
30 mathematical models (e.g. BOADICEA, BRCAPRO, Manchester-Scoring-System) or through
31 standardized clinical-criteria to identify individuals who fulfil this probability threshold and can be
32 offered genetic-testing. Identification of unaffected carriers is important given the high risk of
33 cancer in these women and the effective options available for clinical management which can
34 reduce cancer risk, improve outcomes and minimise burden of disease. Risk-reducing salpingo-
35 oophorectomy (RRSO) once the family is complete is the most effective option to reduce ovarian
36 cancer (OC) risk. Taking the combined contraceptive-pill can reduce OC-risk by half. Risk-reducing
37 mastectomy (RRM) is the most effective option for reducing breast cancer (BC) risk. Additionally
38 high-risk women can opt for chemoprevention with selective estrogen-receptor-modulators
39 (SERM) as well as early-onset annual MRI/mammography screening. Carrier identification also
40 offers the opportunity for making informed reproductive and contraceptive choices affecting
41 cancer risk, including timing of having children, pill-use, and pre-implantation genetic-diagnosis
42 (PGD). In women affected by cancer it offers the choice of targeted therapy using drugs like PARP-
43 inhibitors to improve survival as well as access to novel clinical trials. Additionally unaffected
44 family members can be identified through cascade-testing and offered options of
45 screening/prevention.

46 This clinical-criteria/FH based approach has numerous limitations. While moderately effective at
47 identifying individuals with mutations, it is poor at ruling out the presence of one. We¹ and others²,
48 ³ have shown current testing criteria miss >50% *BRCA*-carriers. Thus, even if working at 100%
49 efficiency half the carriers at high-risk of cancer cannot be identified by the current clinical

50 approach. Data suggest that over 80% patients fulfilling clinical-criteria for genetic-testing have
51 never discussed this with a health-professional. Another drawback is the need for an individual in
52 a family to develop cancer before others who are unaffected can be identified. Why should we
53 need to wait for this to happen? Despite over two decades of testing, only 3% of estimated carriers
54 in the population have been identified.⁴ Limited public and health professional awareness,
55 coupled with the complexity and inefficiencies of a gate keeper driven testing pathway/service
56 structure has resulted in restricted access and under-utilisation of genetic-testing across all health
57 systems.⁵ Continuing at the current rates of identification, we will never identify even the 50% of
58 the estimated residual pool of carriers in the population who fulfil testing criteria, let alone the
59 unidentifiable half. Even doubling current rates will warrant ~165 years to identify these 50% at-
60 risk individuals.⁴ Incorporation of mainstreaming into clinical practice will improve detection rates
61 and identify those lacking a strong FH but still requires individuals to develop cancer before
62 unaffected carriers can be identified. Forecasting models suggest addition of mainstreaming to
63 current testing rates will also necessitate ~250 years to identify the entire residual pool of
64 carriers.⁴ Given the huge benefit and opportunity to prevent cancers in unaffected mutation
65 carriers, this questions the adequacy and satisfactoriness of our current clinical approach. Offering
66 unselected population-testing irrespective of FH or cancer diagnosis can overcome the limitations
67 of a clinical-criteria/FH-based approach, provide an impetus to expand and boost identification of
68 unaffected carriers to maximise primary prevention. Falling costs of genetic-testing, use of next-
69 generation-sequencing (NGS) technologies and advances in bioinformatics has provided the
70 technical ability to undertake large-volume mass-scale genetic-testing. Increasing public and
71 media awareness, expanding applicability of genetics as well as the growing evidence base has
72 made this issue prime time.

73 **Population-testing in the Jewish-population**

74 The largest evidence base for population-testing comes from the Jewish population. 1-in-40
75 Ashkenazi Jews carry a *BRCA1/BRCA2* mutation. The Jewish population is the first population for
76 whom population-testing is likely to be introduced in clinical practice. The UK GCaPPS randomised
77 trial as well as cohort studies in Israel and Canada have evaluated population-based *BRCA*-testing
78 in the Ashkenazi-Jewish (AJ) population.¹⁻³ These studies show that unselected population-based
79 *BRCA*-testing in the AJ-population is acceptable, feasible, can be undertaken outside the
80 traditional hospital setting in the community, identifies an equivalent number of additional
81 carriers who do not fulfil standard clinical testing criteria and is associated with high satisfaction
82 rates of 90-95%.^{1, 2, 6} Randomised-trial data indicated that compared to FH-testing population-
83 testing is not associated with an adverse impact on psychological-health or quality-of-life and
84 anxiety and uncertainty decrease with time following testing. Cohort data from Israel and Canada
85 indicate that in mutation carriers there is increased anxiety and distress at 6-months/1-year.
86 Barriers and facilitators of unselected genetic-testing are also similar to those seen in high-risk
87 clinics. Overall the findings from population-testing studies are similar to those reported with
88 clinical-criteria based testing through cancer genetics clinics.

89 Pre-test counselling remains a key pre-requisite to genetic-testing in clinical practice. For
90 population-testing to be feasible, newer approaches for delivering pre-test information are
91 needed to facilitate informed decision making. An AJ UK non-inferiority cluster-randomised trial,
92 found that DVD-based pre-test counselling for population *BRCA*-testing was non-inferior with
93 respect to knowledge gained, satisfaction, risk perception and equivalent for testing uptake as
94 well as being time-saving and cost-efficient compared to standard/1:1 face-to-face genetic-
95 counselling.⁷ RCT data show that telephone-counselling is also non-inferior to traditional genetic-
96 counselling. *BRCA*-testing without pre-test counselling was undertaken successfully in the Israeli
97 and Canadian population-based studies with high satisfaction rates of 91-95%. The only post-test
98 counselling approach has not yet been compared to standard 1:1/telephone-based/DVD-based
99 pre-test counselling in a RCT.

100 Three cost-effectiveness analyses have evaluated population-based *BRCA*-testing in the Jewish-
101 population. AJ-population based *BRCA*-testing is extremely cost-effective for both UK and US
102 health-systems and is in fact cost-saving in most scenarios.^{8, 9} *BRCA*-mutations occur in the
103 Sephardi-Jewish population at a lower frequency of 1-in-100 than the AJ-population (1-in-40).
104 However, this approach is extremely cost-effective in the Sephardi-population too.¹⁰ Population-
105 based *BRCA*-testing in the Jewish-population is one of the few interventions in medicine that can
106 save both lives and money for the health-system. Overall data support changing the paradigm to
107 population based *BRCA*-testing in the Jewish population.

108 **Population-testing in the General-population and Panel genetic-testing**

109 Adoption of NGS by genetic-testing laboratories has led to implementation of panel-genetic
110 testing for multiple cancer-susceptibility-genes (CSGs) in clinical practice. This offers the prospect
111 for population-testing of multiple CSGs. Testing for newer moderate-risk genes like
112 *RAD51C/RAD51D/BRIP1* (OC-risks= 6-11%) and *PALB2* (BC-risk= 44%) has now been implemented
113 and options for OC and BC risk-reduction are available for these gene-mutation carriers. RRSO is
114 cost-effective at ≥ 4 -5% OC-risk,^{11, 12} providing clinical-utility for testing for these newer moderate
115 OC-risk genes and unaffected carriers are now offered surgical prevention. Annual MRI/risk-
116 reducing mastectomy is available to women at >40 % risk. *MLH1/MSH2/MSH6* mismatch-repair
117 (MMR) gene mutation carriers have an increased risk of colorectal-cancer (40-60%), endometrial
118 cancer (30-40%) and OC (6-14% risk). Effective options for minimising risk for them include 1-2
119 yearly colonoscopies, chemoprevention with aspirin or preventive hysterectomy and bilateral
120 salpingo-oophorectomy. All these genes can be introduced in a general-population testing panel.
121 General-population surveys of UK women suggest that 75% would find population-testing for OC
122 gene mutations for risk-stratification acceptable. Following OC/BC risk disclosure 72% may adopt
123 a positive change in health behaviour. The feasibility of general-population panel-testing for OC
124 gene mutations has been demonstrated in an ongoing pilot-trial (ISRCTN54246466) in London.

125 Women were recruited through primary-care using a web-based decision-aid along with a
126 telephone helpline. In 'The Screen Project' (<http://www.thescreenproject.ca/>) study general-
127 population *BRCA*-testing is being offered to Canadian men/women >18 years through a self-paying
128 direct-to-consumer testing model. We recently showed that population-based panel-testing for
129 OC/BC gene mutations could be cost-effective for the US and UK health-systems. A population-
130 based panel-testing approach is more cost-effective and can prevent thousands more cancers
131 than current clinical-criteria/FH driven *BRCA* or panel genetic-testing strategies. The ICER
132 (incremental cost-effectiveness ratio) were well below the £30,000/QALY (ICER=
133 £21,599.96/QALY) UK and \$100,000/QALY (ICER=\$54,769.78/QALY) USA willingness-to-pay
134 thresholds and sensitivity-analyses demonstrated population-testing to remain cost-effective
135 over 84% and 93% simulations for UK and US health-systems respectively.

136 **Population risk-stratification**

137 Newer risk-prediction models incorporating validated single-nucleotide-polymorphisms (SNPs) as
138 a polygenic-risk score along-with epidemiologic/clinical information have improved precision of
139 risk-estimation enabling population division into risk-strata, which allows targeted risk-stratified
140 screening and/or prevention for those at increased-risk. Studies for risk-stratified
141 breast/ovary/prostate cancer screening incorporating epidemiologic, mammographic-density and
142 SNP data are now being undertaken. The UK PROCAS (UKCRN-ID 8080) study has demonstrated
143 the ability for improved BC-risk prediction (adding SNPs and mammographic-density to the Tyrer-
144 Cuzick model) and risk-stratified BC-screening within the NHS Breast-Screening-Programme.¹³ The
145 ongoing PROMISE Feasibility-Study (ISRCTN54246466) evaluates feasibility and acceptability of
146 using a risk-prediction model (incorporating SNP-profile, panel-genetic-testing and
147 epidemiological data) for OC-risk stratification and subsequent management including
148 prevention.¹⁴ More research/trials evaluating risk-model based stratified screening/prevention,

149 clinical effectiveness, impact, cost-effectiveness, health-behaviour, psychological/social
150 consequences are needed.

151 **Summary**

152 There is convincing evidence to support change in paradigm to population testing in the Jewish-
153 population. Additionally there is a strong rationale for extending this to the non-Jewish general-
154 population to maximise prevention. Supporting evidence for extending this to the broader
155 general-population is now emerging. Further data are needed with respect to impact of panel-
156 testing in a general-population. Additional data are needed with respect to uptake of downstream
157 screening and prevention in individuals without a strong FH of cancer to re-confirm overall cost-
158 effectiveness. While the majority of variants-of-uncertain-significance (VUS) identified through
159 genetic-testing are benign and will not be of any significant consequence, a small proportion of
160 class-III VUS may get re-categorised in the future into pathogenic mutations. Hence, we will also
161 need further research into impact of VUS, long-term management and monitoring of VUS and
162 development of pathways for this. This raises an urgent need for implementation studies into
163 general-population panel-testing. As further validation of absolute cancer risk models
164 incorporating epidemiologic, SNP, and other genetic/non-genetic data emerge, these can be used
165 to better stratify the population for targeted screening and prevention. This too could eventually
166 be incorporated into a future population-testing strategy. Whilst population-testing for cancer
167 genes is now reaching prime-time, this strategy could also be adopted for preventing other chronic
168 diseases in the future. Data and experience from a cancer prevention population-testing strategy
169 could also help inform approaches for prevention of other chronic diseases. The five prime causes
170 of deaths from chronic-disease are heart-disease, cancer, lung-disease, accidents and strokes. The
171 increasing prevalence of chronic-disease is the biggest challenge facing most health-systems,
172 including the NHS. In the UK these are responsible for 70% of the healthcare expenditure, 50% GP
173 appointments and 70% hospital admissions. Reducing chronic-disease burden is key for future

174 financial viability of our health system(s). Population-testing provides a new paradigm to steer
175 healthcare towards prevention for reducing the burden of cancer and potentially other chronic
176 disease.

177 **Disclosure of Interests**

178 RM declares research funding from The Eve Appeal and Cancer Research UK into population
179 testing and from Barts & the London Charity and Rosetrees Trust outside this work, as well as an
180 honorarium for grant review from Israel National Institute for Health Policy Research. FG declares
181 no conflict of interest.

182 **Contribution to authorship**

183 Initial draft of manuscript: RM

184 Manuscript writing and approval: RM, FG

185 **Funding**

186 No funding was received for this commentary.

187

188 **References**

- 189 1. Manchanda R, Loggenberg K, Sanderson S, Burnell M, Wardle J, Gessler S, et al. Population
190 testing for cancer predisposing BRCA1/BRCA2 mutations in the Ashkenazi-Jewish community: a
191 randomized controlled trial. *J Natl Cancer Inst.* 2015 Jan;107(1):379.
- 192 2. Gabai-Kapara E, Lahad A, Kaufman B, Friedman E, Segev S, Renbaum P, et al. Population-
193 based screening for breast and ovarian cancer risk due to BRCA1 and BRCA2. *Proc Natl Acad Sci U S*
194 *A.* 2014 Sep 30;111(39):14205-10.
- 195 3. Metcalfe KA, Poll A, Royer R, Llacuachaqui M, Tulman A, Sun P, et al. Screening for founder
196 mutations in BRCA1 and BRCA2 in unselected Jewish women. *J Clin Oncol.* 2010 Jan 20;28(3):387-91.
- 197 4. Manchanda R, Blyuss O, Gaba F, Gordeev VS, Jacobs C, Burnell M, et al. Current detection
198 rates and time-to-detection of all identifiable BRCA carriers in the Greater London population. *J Med*
199 *Genet.* 2018 Apr 5.
- 200 5. Childers CP, Childers KK, Maggard-Gibbons M, Macinko J. National Estimates of Genetic
201 Testing in Women With a History of Breast or Ovarian Cancer. *J Clin Oncol.* 2017 Dec 1;35(34):3800-
202 6.
- 203 6. Metcalfe KA, Poll A, Llacuachaqui M, Nanda S, Tulman A, Mian N, et al. Patient satisfaction
204 and cancer-related distress among unselected Jewish women undergoing genetic testing for BRCA1
205 and BRCA2. *Clin Genet.* 2010 Nov;78(5):411-7.
- 206 7. Manchanda R, Burnell M, Loggenberg K, Desai R, Wardle J, Sanderson SC, et al. Cluster-
207 randomised non-inferiority trial comparing DVD-assisted and traditional genetic counselling in
208 systematic population testing for BRCA1/2 mutations. *J Med Genet.* 2016 Jul;53(7):472-80.
- 209 8. Manchanda R, Legood R, Burnell M, McGuire A, Raikou M, Loggenberg K, et al. Cost-
210 effectiveness of population screening for BRCA mutations in Ashkenazi jewish women compared
211 with family history-based testing. *J Natl Cancer Inst.* 2015 Jan;107(1):380.

- 212 9. Manchanda R, Patel S, Antoniou AC, Levy-Lahad E, Turnbull C, Evans DG, et al. Cost-
213 effectiveness of population based BRCA testing with varying Ashkenazi Jewish ancestry. Am J Obstet
214 Gynecol. 2017 Nov;217(5):578 e1- e12.
- 215 10. Patel S, Legood R, Evans DG, Turnbull C, Antoniou AC, Menon U, et al. Cost effectiveness of
216 population based BRCA1 founder mutation testing in Sephardi Jewish women. Am J Obstet Gynecol.
217 2018 Apr;218(4):431 e1- e12.
- 218 11. Manchanda R, Legood R, Antoniou AC, Gordeev VS, Menon U. Specifying the ovarian cancer
219 risk threshold of 'premenopausal risk-reducing salpingo-oophorectomy' for ovarian cancer
220 prevention: a cost-effectiveness analysis. J Med Genet. 2016 Sep;53(9):591-9.
- 221 12. Manchanda R, Legood R, Pearce L, Menon U. Defining the risk threshold for risk reducing
222 salpingo-oophorectomy for ovarian cancer prevention in low risk postmenopausal women. Gynecol
223 Oncol. 2015 Dec;139(3):487-94.
- 224 13. Evans DG, Astley S, Stavrinou P, Harkness E, Donnelly LS, Dawe S, et al. Improvement in risk
225 prediction, early detection and prevention of breast cancer in the NHS Breast Screening Programme
226 and family history clinics: a dual cohort study. Programme Grants for Applied Research.
227 Southampton (UK): NIHR Journals Library; 2016.
- 228 14. PROMISE FS. Predicting risk of ovarian malignancy improved screening and early detection:
229 Feasibility study Biomed Central; 2017. p. DOI 10.1186/ISRCTN54246466
230 <http://www.isrctn.com/ISRCTN>.