Population based genetic testing for cancer susceptibility genes: quo vadis

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Ovarian cancer, breast cancer, endometrial cancer, and colorectal cancer account for ~50% of cancers in women.[1] 2.9M women worldwide and ~88,000 UK-women are diagnosed with these cancers annually and 1.05M women worldwide and 25,000 UK-women per year die from them.[1, 2] GLOBOCAN predicts the number of these cancer cases will rise by 27%-53% worldwide (by 20%-36% in UK-women) and deaths by 49%-69% worldwide (by 36%-47% in UK-women) over the next 20 years.[2] 'Pathogenic and likely pathogenic variants' , here-forth called 'Pathogenic-variants' or 'PVs', in a number of high-moderate penetrance cancer susceptibility genes (CSGs) can cause high-risk breast and/or ovarian cancer syndrome; or Lynch Syndrome (caused by mismatch-repair genes). High-risk breast and ovarian cancer syndrome is associated with an increased risk of developing BC and/or OC. Lynch Syndrome is associated mainly with an increased risk of endometrial cancer, colorectal cancer and ovarian cancer (see Table-1). Overall, CSGs account for around 15%-20% ovarian cancers,[3] 4% breast cancers,[4] 3% endometrial cancers[5] and 3-4% colorectal cancers[6, 7]; and a majority of these cancers are potentially preventable. High-risk breast and ovarian cancer, and Lynch syndromes fall under Tier-1 genomic applications, defined by Centers for Disease Control and Prevention and the Office of Public Health Genomics, as those having significant potential for positive impact on public health based on existing evidence-based guidelines and recommendations. Effective preventive therapy options including risk reducing surgery (mastectomy, risk-reducing salpingo-oophorectomy (RRSO), hysterectomy), chemoprevention (for example aspirin or selective estrogen receptor modulators) and screening (for women at high-risk of breast or colorectal cancers), to reduce these CSG carriers' associated cancer risks are available in the UK National-Health-Service (NHS) and other health-systems (Table-1). Women can also make lifestyle, contraceptive & reproductive choices including pre-natal/preimplantation genetic diagnosis, all of which can impact cancer risk.

The traditional model of genetic testing to identify CSG carriers involves accessing genetic testing through high-risk cancer genetics clinics/services and is based on fulfilling a strong three generational family-history or standardized clinical criteria. This process is complex, can vary regionally and internationally, and has been shown to be hampered by limited public and health professional awareness, restricted access, inadequate uptake and huge underutilisation of genetic testing. Besides family-history/clinical-criteria are only moderately effective at identifying PV carriers and have extremely poor NPV (ability to rule out a PV-carrier).[8] Additionally, the traditional genetic-testing thresholds have been set too high (e.g. 10% combined probability for '*BRCA1 and BRCA2*' testing). We and others have shown that around 50% of breast and ovarian CSG carriers do not fulfil current clinical/family-history based genetic-testing criteria and are missed.[3, 9, 10] Far greater numbers of carriers are missed through population-based ascertainment.[11] For Lynch Syndrome, Bethesda molecular criteria and Amsterdam-II clinical criteria miss, 12-30% and 55-70% of carriers respectively.[5] Recent data show that traditional family-history guidelines may further magnify health inequalities for minority communities like non-Hispanic Black populations, by identifying proportionally fewer high-risk women in these populations.[12] We showed that despite 25 years of a well-structured clinical genetics delivered national service, free at the point of care, over 97% of *BRCA*-carriers remain undetected in a 16million London population.[13] Forecasting models suggest current detection rates are inadequate, and even doubling rates would take 165-years to identify the 'clinically detectable' proportion of *BRCA*-carriers with 50% remaining unidentifiable as they don't fulfil testing criteria. Given the effective risk management including screening (for breast/colorectal cancer) and preventive therapy options available for CSG carriers, this highlights the inadequacy of our current approach and the massive scale of missed opportunities for cancer prevention. Next-generation sequencing technologies, falling costs, advancements in bioinformatics, our increasing understanding and applicability of genetics coupled with rising public awareness, now permits large scale, high throughput population-based genetic-testing ("population-testing"). *Why should we wait for someone to develop cancer in order to identify people in whom we can prevent cancer?*

Identifying a woman as a CSG-carrier after she develops cancer is a failure of cancer prevention!

Changing paradigm to population-testing can address the limitations above of the current clinical genetic-testing model for CSGs across health systems and provides a forward looking strategy to maximise precision prevention. Precision prevention encompasses a prevention strategy which incorporates individual variation in genetic, epigenetic and non-genetic (environmental, hormonal, reproductive, lifestyle) factors. Half a century ago Wilson-&-Jungner provided the initial guiding principles for population-testing for disease.[14] These have been modified over the years and the UK National Screening Committee has established criteria for UK screening programmes. Over the years additional adaptations to these principles have been developed for screening for genetic susceptibility, including important principles such as 'analytic-validity, clinical-validity, clinical-utility and associated ethical, legal and social implications' (ACCE framework)[15] and other modifications. Development of any population-testing framework needs to consider both benefits and harms and only include testing for CSGs with well-established clinical-utility. There should be effective interventions to reduce cancer risk and the risk conferred by the CSGs should lie above the risk-thresholds for undertaking these interventions. For example RRSO is now recommended for women at >4-5% lifetime OC-risk in the UK,[16] or >3-4% lifetime OC-risk in the USA,[17] thus providing clinical-utility for testing newer moderate penetrance CSGs.

The Jewish model for Population-based genetic testing (population-testing)

The greatest wealth of data supporting population-testing comes from *BRCA*-testing in the Jewish population. Around 1 in 40 Ashkenazi Jewish (AJ) individuals carry one of three Jewish *BRCA* founder-mutations.[9, 18] Our UK randomised trial (GCaPPS) showed that population-based *BRCA*-testing (compared to family history-based testing) in the AJ-community is feasible, acceptable, safe, has high satisfaction, does not harm quality-of-life or psychological well-being, reduces long term anxiety, reduces uncertainty, more than doubles the *BRCA*-carriers identified,[9, 19] and can be

delivered in a community setting. These findings are corroborated and complemented by data from large cohort studies from Israel, Canada, Australia and the USA.[18, 20] Jewish population *BRCA*-testing has been demonstrated to be extremely cost-effective and in fact is cost-saving in most scenarios.[21] 10% of breast cancers[22] and 40% ovarian cancers[23] in the Jewish population are due to *BRCA* founder-mutations and potentially preventable. We and others have long advocated changing policy to offer population-based *BRCA*-testing in the Jewish community. Consequently, Israel has recently changed policy and now offers population *BRCA* founder-mutation testing to all Jewish individuals. Pilot sites offering Jewish-population *BRCA*-testing are expected to be implemented in the UK health service in 2023. The Jewish population is the first population worldwide to undergo population-testing in a clinical/healthcare setting.

Biobanks/ Genomic population cohorts

Additional secondary findings including PVs in CSGs, have been returned to patients/populations recruited to large biobanks and/or population cohorts, for example UK-Biobank, 100,000 Genomes, Geisenger MyCode Initiative, LifePool Study and Healthy Nevada Project. While these data are complementary, add to the increasing evidence base, and address the population PV prevalence for established CSG; this 'bolt-on' return of additional 'secondary-findings' undertaken is not equivalent to prospective uptake of testing CSGs in an unselected unaffected population. A selective sub-group opting for return of incidental/ secondary looked-for findings is not generalizable to an unselected unaffected general population. Post-hoc sequencing and/or analysis does not address in a prospective unbiased fashion key issues and problems related to the (i) logistics of population-testing, (ii) information-giving, consent, uptake-of testing, (iii) uptake of screening and preventive options (iv) Variants-of-Unknown Significance management, (v) long-term outcomes.

Population-testing in the general population

Findings from the AJ population cannot be directly extrapolated to the non-Jewish general

population. The Canadian 'Screen Project' provided a direct-to-consumer *BRCA* -testing option in the general-population, and has been the first of its kind. However, participants (rather than the health system) were expected to pay for their test through out of pocket costs. 1269 individuals were tested over 2 years. While this approach may be helpful for improving access for some, a health system funded population screening programme is what is needed to maximise uptake, ensure equity of access, downstream management and maximise population impact. We demonstrated the potential cost-effectiveness and beneficial population impact of population *BRCA*-testing across multiple high-income, upper-middle income country health systems.[24] This approach is potentially cost-saving for Netherlands, USA and cost-effective for the UK, Brazil and China.[24] The cost of testing needs to fall further for it to be cost-effective in low-income countries like India.[24] This strategy can prevent tens of thousands more breast and ovarian cancer cases compared to current clinical strategies. We estimate the total general population prevalence of Tier-1 CSGs associated with *BRCA1/BRCA2/PALB2/RAD51C/RAD51D/BRIP1/MLH1/MSH2/MSH6/PMS2* CSGs listed in Table-1 to be around 1.3%.[25, 26] Data from large biobank/cohort studies show that ~75% of CSG carriers do not fulfil traditional family history-based clinical-criteria and would be missed.[11] Relatives of PV-carriers identified can undergo cascade testing. Unaffected relative PV carriers identified through cascade testing can also avail of risk management and preventive interventions (Table-1). Not all CSG carriers identified will develop cancer as these have variable penetrance. All at risk individuals should have informed counselling of the pros and cons of risk-management options including surgical prevention. Undergoing preventive surgery can be a complex and difficult decision making process, which changes with time. Different individuals may opt for it at different time points and some may make an informed choice not to undergo it. Expanding on our earlier modelling with current clinical uptake rates for surgical prevention,[24, 25] we estimate that testing 10,000 women could potentially lead to preventing a composite estimate of ~210 breast/ovarian/endometrial/colorectal cancers. We previously showed the cost-effectiveness of population-based testing for a panel of Tier-1 high-risk breast/ovarian CSGs genes (*BRCA1/BRCA2/RAD51C/RAD51D/BRIP1/PALB2*) in UK and USA

155 healthcare settings (ICER= £21,599.96/QALY or $54,769.78/QALY), with 83.7% and 92.7% of
156 simulations being cost-effective on probabilistic sensitivity analysis.[25] Potential cost-effectiveness for
157 *BRCA1/BRCA2/MLH1/MSH2/FXS/CF* has been highlighted for the Australian population too.[27]
158
159 Complex risk models incorporating genetic, family history, epidemiologic and clinical variables are
160 now being used to predict personalised absolute cancer risk. These have been developed and
161 validated for a number of cancers including, breast, ovarian and endometrial cancers. While good
162 validation data is available for breast cancer and beginning to emerge for ovarian cancer, more
163 robust validation data is needed for other cancers. This approach enables population stratification
164 for risk adapted screening and/or risk adapted prevention. Breast cancer risk models incorporating a
165 Single-Nucleotide-Polymorphisms-(SNP)-based polygenic-risk-score (PRS), mammographic density
166 and epidemiologic variables are currently being used to implement risk adapted BC screening in
167 large scale population cohorts (UK PROCAS study) and clinical trials such as WISDOM (USA), MyPeBS
168 (European). Our pilot population-testing study to predict personalised OC-risk using a validated OC-
169 risk model incorporating CSGs, polygenic-risk-score and epidemiologic/reproductive risk-factors,
170 recruited women through primary-care using a web-based decision tool, and demonstrated
171 feasibility, acceptability, high satisfaction and reduction in cancer-worry with this approach.[28]
172
173 More real world multidisciplinary implementation studies are needed to evaluate the impact of
174 population-testing for CSGs. Research needs to evaluate the psychological and socio-ethical
175 outcomes of population-testing. While initial modelling has highlighted potential cost-effectiveness
176 of this approach, real world studies with long-term outcomes of screening and prevention are
177 needed to confirm that the model assumptions are valid and will translate to patient benefit and
178 reduction in cancer incidence, reconfirming cost-effectiveness. It is likely that population-testing
179 implementation models will vary by country and health system as they will need to be context
180 specific, while following the common core principles of population-testing (see Figure-1 for an

example). Simplification and mainstreaming of such large scale testing will require digitisation of the process of information giving, consent, and a direct-to-patient (saliva based) testing approach, with more intensive counselling and support reserved for those testing positive.

Other challenges that need to be tackled include a method for management of Variants-of-Unknown Significance, and developing a structure or framework for safe data management, data protection, consenting and delivery of results. Subsequent scaling up for implementation across the health system will have additional challenges including stakeholder engagement, awareness campaigns, expansion in health workforce infrastructure, laboratory/testing services and downstream screening and prevention infrastructure. The future potential for population-testing to maximise precision prevention globally across high-income, middle-income and low-income health systems is exciting and bright. The costs of genetic-testing have fallen 10 fold over the last decade. While currently cost-effective for high/middle income countries, a price point of ~$100 a test can make this approach potentially affordable in low income countries too. We believe this will be achievable in the future.

Two prospective general population-testing studies are being implemented over the next year which will provide an initial evidence-base for assessment of population-testing. The Australian "DNA screen pilot study" will recruit 10000 healthy individuals between 18-40 years through social media and offer testing for high-risk breast/ovarian cancer, Lynch syndrome and familial hypercholesterolemia CSGs.[29] Our UK "PROTECT" (Population based germline testing for early detection and cancer prevention) trial will evaluate the impact of implementing a population-based panel genetic-testing strategy for high and moderate penetrance high-risk breast/ovarian cancer, Lynch syndrome CSGs in >5000 women >18 years recruited through primary care using a web-based digitally enabled direct-to-patient saliva based DNA-testing approach. PROTECT will address current knowledge gaps for population-testing by evaluating the incremental PVs detected, uptake of testing, acceptability, satisfaction, psycho-social well-being, overall impact, socio-ethics, a Variants-

206 of-Unknown Significance management strategy, long-term uptake of screening and prevention

207 interventions, and health-economic outcomes of population-based genetic testing.

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210 **Table/figure caption list:**

211 Table-1: Tier-1 syndromes, cancer susceptibility genes, cancer risks and management options

212 Figure-1: Population based testing pathway

213

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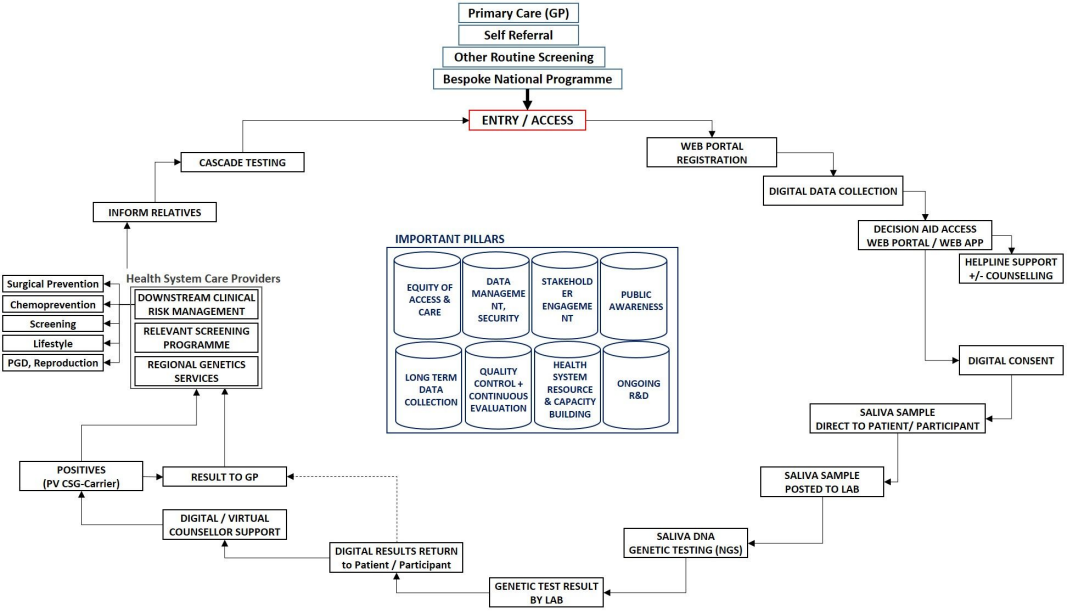
Primary Care (GP)
Self Referral
Other Routine Screening
Bespoke National Programme
ENTRY / ACCESS
CASCADE TESTING
INFORM RELATIVES
WEB PORTAL REGISTRATION
DIGITAL DATA COLLECTION
DECISION AID ACCESS WEB PORTAL / WEB APP
HELPLINE SUPPORT +/- COUNSELLING
DIGITAL CONSENT
SALIVA SAMPLE DIRECT TO PATIENT/ PARTICIPANT
SALIVA SAMPLE POSTED TO LAB
SALIVA DNA GENETIC TESTING (NGS)
GENETIC TEST RESULT BY LAB
DIGITAL RESULTS RETURN to Patient / Participant
DIGITAL / VIRTUAL COUNSELLOR SUPPORT
POSITIVES (PV CSG-Carrier)
RESULT TO GP
IMPORTANT PILLARS
EQUITY OF ACCESS & CARE
DATA MANAGEMENT, SECURITY
STAKEHOLDER ENGAGEMENT
PUBLIC AWARENESS
LONG TERM DATA COLLECTION
QUALITY CONTROL + CONTINUOUS EVALUATION
HEALTH SYSTEM RESOURCE & CAPACITY BUILDING
ONGOING R&D
Health System Care Providers
Surgical Prevention
Chemoprevention
Screening
Lifestyle
PGD, Reproduction
DOWNSTREAM CLINICAL RISK MANAGEMENT
RELEVANT SCREENING PROGRAMME
REGIONAL GENETICS SERVICES

Table-1: Tier-1 syndromes, cancer susceptibility genes, cancer risks and management options

		Cancer Risks %				Risk Management Options				
	GENES	**BC**	**OC**	**CRC**	**EC**	**BC**	**OC**	**CRC**	**EC**	**Other**
HBOC- **High risk breast &/or ovarian cancer syndrome**	**BRCA1**	**72**	**44**			**RRM, Chemoprevention (SERM, Aromatase inhibitors), *Screening (MRI, Mammogram)**	**RRSO RRESDO**			**Lifestyle Reproduction Contraception PND PGD**
	BRCA2	**69**	**17**							
	PALB2	**53**	**5**							
	RAD51C	**21**	**11**			***Screening (Mammogram)**				
	RAD51D	**20**	**13**							
	BRIP1		**6**							
LS- **Lynch Syndrome**	**MLH1**		**11**	**48**	**37**		**Hysterectomy & BSO**	**Screening (Colonoscopy) Chemoprevention (Aspirin)** **Surgical Prevention**	**Hysterectomy Annual USS, hysteroscopy & endometrial biopsy**	
	MSH2		**17**	**47**	**49**					
	MSH6		**11**	**20**	**41**					
	PMS2**		**3**	**10**	**13**					

*RRM- Risk Reducing Mastectomy; RRSO - Risk reducing Salpingo-oophrectomy; RRESDO - Risk reducing early salpingectomy and delayed oophorectomy; BSO- Bilateral Salpingo-oophorectomy; Hyst- hysterectomy; SERM- Selective Estrogen Receptor Modulators; PGD- Pre-implantation Genetic Diagnosis; PND- Prenatal Diagnosis; CP- chemoprevention. *NHS High risk Breast Cancer Screening Programme.* **BSO is not recommended for *PMS2* as ovarian cancer risk is similar to population level risk