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

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Background

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

This clinical-criteria/FH based approach has numerous limitations. While moderately effective at identifying individuals with mutations, it is poor at ruling out the presence of one. We[1] and others[2, 3] have shown current testing criteria miss >50% *BRCA*-carriers. Thus, even if working at 100% efficiency half the carriers at high-risk of cancer cannot be identified by the current clinical

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

Population-testing in the Jewish-population

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

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

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

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

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

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

Population risk-stratification

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

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

Summary

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

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

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