Population-based Genetic Testing for Precision Prevention

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Abstract

Global interest in genetic-testing for Cancer-Susceptibility-Genes (CSG) has surged with falling costs, increasing awareness and celebrity endorsement. Current access to genetic-testing is based on clinical-criteria/risk-model assessment which uses family-history (FH) as a surrogate. However, this approach is fraught with inequality, massive underutilisation, and misses 50% CSG carriers. This reflects huge missed opportunities for precision-prevention. Early CSG identification, enables uptake of risk-reducing strategies in unaffected individuals to reduce cancer-risk. Population-based genetic-testing (PGT) can overcome limitations of clinical-criteria/FH-based testing. Jewish-population studies show population-based *BRCA*-testing is feasible, acceptable, has high-satisfaction, doesn't harm psychological well-being/quality-of-life and is extremely cost-effective, arguing for changing paradigm to PGT in the Jewish-population. Innovative approaches for delivering pre-test information/education are needed to facilitate informed decision-making for PGT. Different health-systems will need context specific implementation strategies and management pathways, while maintaining principles of population-screening. Data on general-population PGT are beginning to emerge, prompting evaluation of wider implementation. Sophisticated risk-prediction models incorporating genetic and non-genetic data are being used to stratify populations for ovarian-cancer and breast-cancer risk and risk-adapted screening/prevention. PGT is potentially cost-effective for panel-testing of breast-&-ovarian CSGs and for risk-adapted BC-screening. Further research/implementation studies evaluating the impact, clinical efficacy, psychological, and socio-ethical consequences and cost-effectiveness of PGT are needed.

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Since the iconic discovery of the *RB1*, retinoblastoma cancer-susceptibility-gene (CSG) over 100 CSGs and associated syndromes have been described with implications for clinical management. Discovery of *BRCA1-&-BRCA2*, advances in sequencing technologies and bioinformatics along-with increasing societal awareness and celebrity endorsement has heralded a boom in genetic-testing for inherited susceptibility of breast-&-ovarian cancer. *BRCA1/BRCA2* are prime examples of CSGs with well-established clinical-utility, for whom effective clinical interventions of therapeutic benefit are available. Around 10-20% of ovarian-cancer (OC)(1) and 6% breast-cancer (BC)(2) overall, are caused by *BRCA1/BRCA2* mutations. Women carrying *BRCA1/BRCA2* mutations have a 17-44% OC-risk and 69-72% BC-risk till 80-years.(3) Most of these cancers are potentially preventable. Effective enhanced breast-screening (MRI/mammograms), chemoprevention(4,5) and surgical prevention (risk-reducing salpingo-oohorectomy (RRSO), risk-reducing mastectomy (RRM)) strategies(6,7) are available as standard clinical practice. Additionally, early identification of CSG also enables autonomy in family-planning, lifestyle, contraception and reproductive choices affecting risk, including Preimplantation-Genetic-Diagnosis. Access to targeted oncogenetic therapies like Poly-ADP ribose-polymerase (PARP) inhibitors for *BRCA*-mutated tubo-ovarian cancers(8) has led to *BRCA*-testing for all high-grade non-mucinous epithelial-OC,(9,10) and cascade-testing for unaffected family members. Genetic-testing for CSGs to identify unaffected 'at-risk' individuals who can access prevention will arguably provide the greatest impact on burden of cancer rather than targeted therapies..

'Precision Prevention' is a prevention strategy which incorporates individual variation in genetic, epi-genetic and non-genetic (e.g. environment, hormonal, lifestyle, behavioural) factors. This comprises both primary-prevention to prevent occurrence of disease as well as, secondary-prevention including screening strategies for early-detection of pre-symptomatic and/or sub-clinical forms of disease. Current guidelines and access to genetic-testing/treatment pathways remain complex, vary regionally and internationally, are fraught with inequality and associated with massive under-utilisation of genetic-testing.(11) Typically information from a three-generation family-history (FH) is used along-with

established clinical-criteria or risk-algorithms (e.g. BRCAPRO, BOADICEA, Manchester-Scoring-System, etc.) to detect those whose mutation-probability lies above the current clinical threshold for testing (approximately 10% carrier probability for *BRCA*-mutations). Even at 100% efficiency the health-system will miss >50% CSG-carriers as they do not fulfil current testing criteria. Only 20% eligible US-women access and undergo genetic-testing.(11) Despite >25years of testing 97% of estimated *BRCA*-carriers in the UK-population remain unidentified and forecasting models show current rates of testing and carrier identification are inadequate to ever identify the residual pool of *BRCA*-carriers.(12) All this highlights the enormous scale of missed opportunities for precision-prevention. The potential to avoid the emotional/physical turmoil of a cancer diagnosis represents a societal priority. Why do we need to wait for people to get cancer to identify those in whom we can prevent cancer? To detect a CSG-carrier following cancer diagnosis of a potentially preventable cancer is a failure of cancer prevention.

Population-based genetic-testing (PGT), i.e. offering unselected genetic-testing to all (independent of cancer history in self or family) is an alternative strategy which can overcome limitations of a clinical-criteria/FH-based strategy and maximise precision-prevention. The principles of population-testing for disease were originally provided by Wilson-&-Jungner.(13) The UK National-Screening-Committee has developed updated criteria followed for its national screening programmes.(14) Criteria adapted to genetic-susceptibility of disease have been suggested by Khoury(15) and Andermann.(16) The ACCE model based on the key principles of 'analytic-validity, clinical-validity, clinical-utility and associated ethical, legal and social implications' provided a framework of 44 questions for evaluating applicability of a genetic-test.(17) Burke and Zimmerman from the Public-Health-Foundation further built on the ACCE model highlighting an approach for evaluation of a genetic test.(18) It is important these principles are borne in mind while developing our approach towards PGT for precision-prevention. A key premise inherent in a public health screening strategy is it is not designed to identify 'all' individuals with disease, but the large/significant proportion of individuals in a clinically efficient and cost-effective manner while minimising harm.

Testing high-prevalence populations: The Jewish Model

One-in-40 Ashkenazi-Jews (AJ) carry one of three *BRCA* founder-mutations compared to *BRCA*-mutation prevalence of approximately 1–in-200 individuals in the general population. Most of the evidence for PGT currently comes from population-based *BRCA*-testing studies in the Jewish-population. These include a UK-based randomised trial (GCaPPS),(19-22) Israeli(23-25) and Canadian(26,27) cohort studies as well as ongoing Australian (JeneScreen Programme)(28) and US-based (BFOR)(29) studies. There is a wealth of data to show that AJ population-based *BRCA*-testing is feasible, acceptable, has high uptake rates, can be delivered in a community setting (outside a clinic/hospital setting), doubles the *BRCA*-carriers identified, and has high satisfaction rates (90%-95%). Long-term follow-up data do not show adverse impact on psychological-health or quality-of-life.(19,30) Recent RCT-data show lower anxiety with population-testing compared to a FH-based testing.(19) Jewish population-based *BRCA*-testing is highly cost-effective, and cost-saving in most scenarios.(31,32) It fulfils the criteria described for population-screening of disease above. The lack of an established downstream management infrastructure for identified *BRCA*-carriers would be barrier to implementation/adoption of population-testing. The USPSTF sites lack of long-term data on cancer incidence and mortality in *BRCA*-carriers ascertained through population screening as a limitation.(33) However, these data exist in *BRCA*-carriers identified through existing clinical-genetics services outside of population-based ascertainment and there is no reason why these outcomes would be different for additional carriers identified through population-ascertainment. The uptake of screening and prevention interventions following population ascertainment has been demonstrated. The updated NCCN guidelines now support *BRCA* Founder mutation testing in unaffected AJ men/women at population level risk within a medical framework where there is access to pre-test education and post-test counselling.(34) The time has come to change the paradigm to population-testing for the Jewish-population. However, AJ-population findings cannot be generalised to the broader general-population.

Pre-test Education and Counselling

Pre-test education and counselling has been a cornerstone of the clinical genetic-testing process.(35) Providing this effectively on a mass/population scale is critical for delivering PGT. For population-

testing to be feasible, newer approaches for delivering pre-test information are needed to facilitate informed decision-making. The best modality to deliver pre-test education in the context of PGT is unresolved. We don't feel there will be a one-size fits all model. Whether formal pre-test counselling is needed remains uncertain. Within the Jewish-model of PGT both Israeli and Canadian studies challenged its value, by providing only 'pre-test information' and post-test genetic-counselling for mutation carriers, with high satisfaction rates (>90%).(26,36) However, ~20% participants and up-to 56% carriers indicated they would have preferred to have had pre-test counselling.(24,26) The UK AJ trial provided formal pre-test counselling within population-testing and found DVD-assisted counselling to be non-inferior and more time and cost-efficient to traditional face-to-face counselling.(21) Pre-test counselling increased awareness of disadvantages/limitations of *BRCA*-testing, influencing final cost-benefit perception and decision-making on undergoing testing.(20) Various clinical-models have shown Telephone-counselling, group-counselling and tele-genetic counselling are non-inferior to standard/traditional face-to-face counselling.(37,38) The Australian JeneScreen project(28) and a UK population-based pilot-study have evaluated an online web-based decision-aid (along-with an optional telephone-helpline) pre-test education and consent process, showing feasibility of this approach.(39) However, RCT-data comparing this to one of the standard pre-test counselling approaches are unavailable. A web-based direct to patient model remains an attractive option going forward. The USPSTF highlights the need for identifying which genetic counselling strategy is most effective and will increase access in rural/other settings as an important research gap.(40) Different health-systems will need to develop context specific workable implementation strategies for pre-test education, and pre/post-test counselling/management, while maintaining the principles of population-screening.

Testing low-prevalence populations: The General-Population Model

PGT in the general-population offers the opportunity for precision-prevention on a much larger scale and initial data related to this are beginning to emerge. However, lower prevalence as well as socio-cultural variations within the general-population represent new challenges and prevent direct extrapolation from the AJ-findings. While selecting CSGs for PGT, the ACCE principles should be

followed, and only genes with well-established clinical-utility tested for. We are against indiscriminate large-scale commercial panel testing without clear clinical benefit/utility and advocate against it. A potential panel of genes could include *BRCA1, BRCA2, PALB2, RAD51C, RAD51D, BRIP1, MLH1, MSH2, MSH6* and *EPCAM*. The analytic-validity and clinical-validity of these tests are established. The clinical-utility for these is confirmed by their risks lying above the threshold for clinical intervention and there being effective clinical interventions available for these CSGs to manage/reduce risk. The issue of lower penetrance through population-based ascertainment has been highlighted by some. However, number of studies demonstrate that breast/ovarian cancer penetrance for *BRCA1/BRCA2* carriers identified through population-testing and those without a strong FH are also 'high', though as expected these estimates are a bit lower than those obtained from individuals attending cancer genetic clinics.(3,23,41-43) The cancer risks remain well above the risk-thresholds for clinical intervention. More data are needed on the 'Ethical, legal and social implications ('E') of PGT for CSGs. Prospective data on impact of PGT on psychological well-being, quality-of-life, long-term health behaviour, lifestyle in general-population women/men are lacking. A strategy for management of variants-of-unknown significance (VUS) is important and needs developing. Concerns have been expressed at un-necessary treatment or screening/preventive intervention(s) being undertaken for VUS alone. However, there is acceptance in clinical practice that for a VUS (class-3 variant), no clinical action should be taken based on that variant alone.(44) The USPSTF currently recommends against PGT for CSGs in the general-population.(40) The low incidence of moderate penetrance genes, the need for more data on clinical significance of pathogenic variants in multigene panels, need for identifying the best counselling/implementation strategy and the lack of long-term clinical outcome data following general-population testing are knowledge-gaps cited by the USPSTF for currently recommending against unselected genetic-testing in the general-population.(33,40)

A few large genomic/population study cohorts have returned additional 'secondary-findings' as a 'bolt-on' paradigm.(45-48) This is not the same as prospective uptake of testing CSGs of established clinical-utility in an unselected unaffected population, based on principles of population-screening. They do not address in a prospective unbiased fashion the questions of logistics of population-testing,

information-giving, a-priori informed consent, uptake-of testing, uptake-of preventive options. Many challenges remain and need addressing in the development of future approaches to PGT and the delivery of supporting health services.

General-population surveys suggest that 75% UK-women would find population-testing for OC gene mutations for risk-stratification acceptable and 72% may adopt a positive change in health-behaviour following results.(49,50) The PROMISE-pilot trial has conducted panel multi-gene testing for ovarian CSGs and used a validated risk-prediction algorithm to provide a personalised OC-risk estimate in a low-risk London population.(51) The ongoing Canadian 'Screen Project' provides direct-to-consumer *BRCA1/BRCA2*-testing in the general-population. These trials will provide important initial information on acceptability, feasibility and utility of PGT in a lower-prevalence setting. We have shown that PGT for a panel of breast/ovarian CSGs would be cost-effective for the general-population and prevent tens-of-thousands more cancers than current clinical strategies.(52)

Beyond moderate-high penetrance CSGs, common-genetic-variants called single-nucleotide-polymorphisms (SNPs) contribute further variability to cancer-risk. Risk-modelling incorporating SNPs along-with epidemiological risk-factors with/without moderate-high penetrance CSGs, can be used to stratify population into risk-categories for better targeted precision-prevention. Risk-adapted BC-screening strategies, which incorporate SNP-profile (as a polygenic-risk-score) and mammographic density for improved personalised risk-prediction, better triage, reduced over-diagnosis and improved targeted-screening, are being evaluated in the UK(PROCAS), USA(WISDOM) and Europe(MyPeBS) studies. Modelling suggests this approach could be cost-effective.(53) The maximum improvement of BC-risk with SNP-addition probably comes in the intermediate-risk women, with only small impacts reported in the overall AUC.(54) Machine-learning algorithms may be better at handling multi-dimensional data with increased predictive abilities for complex disease risk than current polygenic-risk-scores.(55) While SNP-profiling represents an important asset to PGT, the clinical, psychological and familial implications of a detecting a pathogenic moderate-high penetrance CSG variant are considerably different and more significant than SNP-testing alone.

Our current healthcare system remains primarily centred on improving disease diagnosis and treatment rather than prevention. Prevention of chronic disease, cancer being the second commonest cause, is a major challenge for our health-systems. PGT for established CSGs can spur increased carrier-detection rates to maximise precision-prevention and reduce cancer burden. Further research and implementation studies evaluating the impact, clinical efficacy, psychological, and socio-ethical consequences and cost-effectiveness of PGT are needed. A key issue that needs addressing is a system for monitoring and managing variants-of-uncertain-significance (VUS) identified during population-screening. All this requires a rigorous multidisciplinary research agenda including cohort-studies and appropriately designed clinical-trials to address knowledge-gaps and develop evidence-based guidelines.(56,57) Moving guidelines into health practice will require public-health campaigns, education programmes, delivery, dissemination, and diffusion research studies.(56) Implementation will require varying levels of workforce expansion/upskilling and reorganisation of health services infrastructure covering all aspects of the genetic-testing and downstream care including screening and prevention pathways. A framework/structure for data management and legal and regulatory protections will need to be established. These changes will need to be system/country and context specific. The potential of PGT for precision-prevention is global, well beyond high-income countries with established genetic services. We feel this approach is likely to be cost-effective in upper-middle income countries. As costs of testing fall we speculate this will be cost-effective in low-middle income countries too. Evaluation of the impact of adoption of evidence-based recommendations and guidelines on real-world health outcomes will be needed.(56) PGT is an exciting and evolving field which offers a new paradigm for precision-prevention in cancer and can also serve as a model for preventing other chronic diseases.

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