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 as a surrogate. However, this approach is fraught with inequality, massive underutilization, 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/family history–based testing. Jewish population studies show population-based *BRCA* testing is feasible, acceptable, has high satisfaction, does not harm psychologic well-being/quality of life, and is extremely cost-effective, arguing for changing paradigm to PGT in the Jewish population. Innovative approaches for delivering pretest 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 nongenetic 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 and ovarian CSGs and for risk-adapted breast cancer screening. Further research/implementation studies evaluating the impact, clinical efficacy, psychologic 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* and *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 and 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 (1) and 6% breast cancer (2) overall are caused by *BRCA1/BRCA2* mutations. Women carrying *BRCA1/BRCA2* mutations have a 17%–44% ovarian cancer risk and 69%–72% breast cancer 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-oophorectomy, risk-reducing mastectomy) strategies (6, 7) are available as standard clinical practice. In addition, 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 PARP inhibitors for *BRCA*-mutated tubo-ovarian cancers (8) has led to *BRCA* testing for all high-grade nonmucinous epithelial ovarian cancers (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, epigenetic, and nongenetic (e.g., environment, hormonal, lifestyle, and behavioral) factors. This comprises both primary prevention to prevent occurrence of disease, as well as secondary prevention including screening strategies for early detection of presymptomatic and/or subclinical 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 underutilization of genetic testing (11). Typically, information from a three-generation family history 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 (~10% carrier

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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 U.S. women access and undergo genetic testing (11). Despite >25 years of testing, 97% of estimated *BRCA* carriers in the United Kingdom 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), that is, 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/family history –based strategy and maximize precision prevention. The principles of population testing for disease were originally provided by Wilson and Jungner (13). The United Kingdom National Screening Committee has developed updated criteria to be followed for its national screening programs (14). Criteria adapted to genetic susceptibility of disease have been suggested by Khoury and colleagues (15) and Andermann and colleagues (16). The ACCE model based on the key principles of "analytic validity, clinical validity, and 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 that these principles are borne in mind while developing our approach toward 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 minimizing harm.

Testing High-prevalence Populations: The Jewish Model

One in 40 Ashkenazi-Jews carry one of three *BRCA* founder mutations compared with *BRCA* mutation prevalence of approximately one 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 United Kingdom–based randomized trial (GCaPPS; refs. 19–22), Israeli (23–25) and Canadian (26, 27) cohort studies, as well as ongoing Australian (JeneScreen Programme; ref. 28) and United States–based (BFOR; ref. 29) studies. There is a wealth of data to show that Ashkenazi-Jews 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 psychologic health or quality of life (19, 30). Recent randomized controlled trial (RCT) data show lower anxiety with population testing compared with a family history–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 U.S. Preventive Services Task Force (USPSTF) sites' lack of long-term data on cancer incidence and mortality in *BRCA* carriers ascertained through population screening is 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 National Comprehensive Cancer Network guidelines now support *BRCA* founder mutation testing in unaffected Ashkenazi-Jews men/women at population-level risk within a medical framework where there is access to pretest education and posttest counseling (34). The time has come to change the paradigm to population testing for the Jewish population. However, Ashkenazi-Jews population findings cannot be generalized to the broader general population.

Pretest Education and Counseling

Pretest education and counseling 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 pretest information are needed to facilitate informed decision making. The best modality to deliver pretest education in the context of PGT is unresolved. We do not feel there will be a one-size-fits-all model. Whether formal pretest counseling is needed remains uncertain. Within the Jewish model of PGT, both Israeli and Canadian studies challenged its value, by providing only "pretest information" and posttest genetic counseling for mutation carriers, with high satisfaction rates (>90%; refs. 26, 36). However, approximately 20% participants and up to 56% carriers indicated they would have preferred to have had pretest counseling (24, 26). The United Kingdom Ashkenazi-Jews trial provided formal pretest counseling within population testing and found DVD-assisted counseling to be noninferior and more time- and cost-efficient to traditional face-to-face counseling (21). Pretest counseling 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

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telephone counseling, group counseling, and tele–genetic counseling are noninferior to standard/traditional face-to-face counseling (37, 38). The Australian JeneScreen project (28) and a United Kingdom population–based pilot study have evaluated an online web-based decision-aid (along with an optional telephone helpline) pretest education and consent process, showing feasibility of this approach (39). However, RCT data comparing this with one of the standard pretest counseling 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 counseling 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 pretest education, and pre/posttest counseling/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 Ashkenazi-Jews 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 are 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, a number of studies demonstrate that breast/ovarian cancer penetrance for *BRCA1/BRCA2* carriers identified through population testing and those without a strong family history are also "high," although, 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" of PGT for CSGs. Prospective data on impact of PGT on psychologic well-being, quality of life, long-term health behavior, and lifestyle in general population women/men are lacking. A strategy for management of variants of unknown significance (VUS) is important and needs development. Concerns have been expressed at unnecessary 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 counseling/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, and 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% United Kingdom women would find population testing for ovarian cancer gene mutations for risk stratification acceptable and 72% may adopt a positive change in health behavior 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 personalized ovarian cancer 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 SNPs contribute further variability to cancer risk. Risk modeling incorporating SNPs along with epidemiologic risk factors with/without moderate–high penetrance CSGs can be used to stratify population into risk categories for better targeted precision prevention. Risk-adapted breast cancer–screening strategies, which incorporate SNP profile (as a polygenic risk score) and mammographic density for improved personalized risk prediction, better triage, reduced overdiagnosis, and improved targeted screening, are being evaluated in the United Kingdom (PROCAS), United States (WISDOM), and Europe (MyPeBS) studies. Modeling suggests this approach could be cost-effective (53). The maximum improvement of breast cancer risk with SNP addition probably comes in the intermediate-risk women, with only small impacts

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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, psychologic, and familial implications of detecting a pathogenic moderate–high penetrance CSG variant are considerably different and more significant than SNP testing alone.

Our current healthcare system remains primarily centered 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 maximize precision prevention and reduce cancer burden. Further research and implementation studies evaluating the impact, clinical efficacy, psychologic and socio–ethical consequences, and cost-effectiveness of PGT are needed. A key issue that needs addressing is a system for monitoring and managing VUSs 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 programs, delivery, dissemination, and diffusion research studies (56). Implementation will require varying levels of workforce expansion/upskilling and reorganization 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.

Disclosure of Potential Conflicts of Interest

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