Population DNA screening for medically actionable disease risk in adults

Australia to take a world-first step towards offering preventive DNA screening through the public health care system

In adult-onset genomic conditions, such as hereditary breast and ovarian cancer (HBOC), Lynch syndrome and familial hypercholesterolaemia, certain DNA variants confer high risk of developing future disease.[1] DNA screening for these conditions could thereby identify medically actionable genetic risk factors, prompting timely risk management and informed decision making from early adulthood to facilitate early detection or prevention.[2] Despite this opportunity, diagnostic rates for these conditions remain low,[2-4] limited by restricted access to genetic testing and lack of awareness.

Collectively, HBOC, Lynch syndrome and familial hypercholesterolaemia affect about one in 75 people or 1.3% of the general population.[1] The United States Centers for Disease Control and Prevention (CDC) recently supported population DNA screening for these conditions (given they meet criteria for population screening), stating that this new approach would have "significant potential for positive impact on public health based on available evidence-based guidelines and recommendations"[5] (Box).

DNA screening for these conditions in Australia would augment existing population-based screening programs, such as BreastScreen and the National Bowel Cancer Screening Program, following the guidelines and principles outlined in the National Population Based Screening Framework.[7] DNA screening would identify younger high risk individuals based on genetic predisposition, optimally before the onset of any disease. These individuals would be managed separately from individuals with early stage cancers or disease precursors identified by other screening programs.

For HBOC, women at high risk are recommended to access regular breast surveillance (mammography, magnetic resonance imaging and/or ultrasound, as clinically indicated) and the option of risk-reducing mastectomy, to reduce breast cancer risk by at least 90–95%.[8] For ovarian cancer, although no effective screening options are available, risk-reducing salpingo-oophorectomy can lower the risk by 80%.[9] Given the poor prognosis following ovarian cancer diagnosis, this procedure can be life-saving. The benefits of identifying HBOC extend to men for early detection and treatment of prostate and male breast cancer. For Lynch syndrome, risk-reduction measures for colorectal cancer include aspirin use and regular colonoscopy, which together can reduce the risk by 60%.[10] Hysterectomy will reduce the risk of endometrial cancer by 90%.[11] For familial hypercholesterolaemia, the risk of premature cardiovascular disease can be managed through statin use and other cholesterol-lowering agents[4] to reduce the risk of myocardial infarction by up to 76%.[12]

Despite the availability of interventions and the ability to identify risk with precision using genomic technology, most high risk individuals for HBOC, Lynch syndrome or familial hypercholesterolaemia remain unidentified.[4,13,14] The prevalence of adults with high risk DNA variants for these conditions (approximately 1.3%)[1] far exceeds the current detection rates via clinical genetic testing, suggesting new approaches are required to increase access to testing. In the absence of Australian data, current criteria-based *BRCA1* or *BRCA2* testing in the United Kingdom is estimated to miss 50–90% of high risk women.[13] Lynch syndrome and familial hypercholesterolaemia detection rates are even lower, with an estimated > 95% of Lynch syndrome[14] and > 90% of familial hypercholesterolaemia high risk individuals remaining unidentified. This is especially significant for younger adults, for whom the preventive potential of genomic testing is greatest. Publicly funded genomic testing for these conditions is currently available only to Australians with disease or family history meeting strict eligibility criteria.[4,14,15] Access to high quality private testing is limited, with high cost and low public awareness of availability. A reliance on self-funded testing increases health inequalities. A criteria-free, population-based approach to genetic testing — population DNA screening using low cost testing for prevention in healthy adults — has the potential to identify far more people at high risk for these conditions. Population DNA screening would also identify high risk individuals earlier, enabling targeted surveillance to commence from a younger age, to facilitate timely prevention or early detection of disease. Once previously unaware high risk individuals have been identified by DNA screening, first degree relatives can also be offered testing for the same DNA change (predictive testing) to identify even more high risk individuals and encourage further surveillance throughout the family. Large pilot studies (N > 10 000 screened participants) are required to address questions relating to ethical and implementation issues, such as informed consent,

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Medically actionable adult-onset genomic conditions[6]

Hereditary breast and ovarian cancer: high risk for breast, ovarian and prostate cancers due to DNA changes in genes that include *BRCA1*, *BRCA2* and *PALB2*[3]

Lynch syndrome: high risk for colorectal, endometrial, ovarian and other cancers due to DNA changes in genes that include *MLH*, *MSH2* and *MSH6*[4]

Familial hypercholesterolaemia: increased risk for coronary heart disease due to DNA changes in genes that include *LDLR*, *APOB* and *PCSK9*, causing very high cholesterol levels from an early age[6]

access to genetic counselling, and clinical management of asymptomatic, apparently high risk individuals without disease family history.

To date, population-based genomic studies have predominantly focused on the *BRCA1* and *BRCA2* genes, including screening of 50 726 US women[16] and 5908 Australian women.[15] Over half of the women identified with *BRCA1* or *BRCA2* DNA changes in these studies were previously unaware of their risk, and did not qualify for criteria-based testing.

Recent DNA-screening programs in the US[1,17] have been made available only to individuals within certain health care networks, living in certain locations (eg, the Healthy Nevada Project in Nevada, and the Geisinger MyCode project in Pennsylvania), and not via a public health care system. This selective approach has not ensured equity of access — a fundamental principle of population-level screening.[7] Pilot studies designed specifically to deliver actionable genomic information as the primary reason for participation, available to all participants at no cost, are required to ensure equity of access, gauge public willingness to participate, and remain consistent with established population screening principles.[7]

Such a study will soon commence in Australia. The DNA Screen pilot study, designed by the DNA Screen Investigator Group and funded by the Medical Research Future Fund Genomics Health Futures Mission, will offer preventive DNA screening for HBOC, Lynch syndrome and familial hypercholesterolaemia to 10 000 Australians aged 18–40 years. The study will address current knowledge gaps in adult population-based DNA screening, and generate new evidence to inform Australia's future. Recruitment will commence in mid-2022. DNA Screen will use innovative online recruitment methods, driven by social media, to ensure socially relevant communication for individuals aged 18–40 years. This age group will benefit most from preventive DNA screening, being old enough to provide informed consent but below the average age of disease onset and the commencement of existing Australian population-based screening programs. The pilot population recruited will be representative of the Australian general population in this age group, by state and territory population size, sex, with diverse cultural and linguistic representation, and Aboriginal and Torres Strait Islander participants. To achieve this, registered individuals will be randomly selected within categories for enrolment until 10 000 participants are recruited. The study will provide clear, video-enhanced information about genetic testing, risk management, implications of a positive and negative result, and other issues via the study website.

Results will be returned to participants using a national, evidence-based telehealth service, which has demonstrated acceptability in previous Australian studies.[18] Participants with high risk screening results (estimated to be approximately 133 individuals out of the 10 000 screened) will be contacted by telephone to explain the results and will be provided genetic counselling. Referrals will be made to relevant state-based clinical services in the public health care system for risk management, and for cascade testing of first degree blood relatives. The high risk genes being tested are incompletely penetrant, meaning not all individuals with high risk variants will develop the associated condition. Clinical services in each state have partnered with the study to ensure that onward management and appropriate downstream support are provided. Participants without high risk DNA changes (about 98% of participants) will be notified electronically, with links to further information provided about the testing conducted and meaning of the results, and access to genetic counselling if requested. After project completion, the primary outcomes (number of index cases, proportion eligible for reimbursed testing, and number of first degree blood relatives presenting for cascade testing) will be reported, and a cost-effectiveness analysis will be provided to the Australian Government for consideration of the possible development of a national adult DNA screening program.

As acknowledged in the Australian Population Based Screening Framework,[7] the balance between ethical concerns and possible harms of a program must be considered. This includes ensuring informed consent and the management of any participant anxiety, either while waiting for results, or for those receiving a high risk result. Our consumer-informed co-design process, and a focus on genetic counselling within and beyond the project, is designed to minimise potential harms while gathering data on consumer preferences and the acceptability of population-based DNA screening in Australia. Further, steps will be taken to ensure participants understand that high risk screening results indicate increased risk, not disease diagnoses. Other identified harms include the potential for genetic discrimination and compromised access to life insurance products.[19] This risk must be weighed by each individual against the potential preventive health benefits of DNA screening, through transparent information provision and informed consent. Increased government

regulation and consumer safeguards are critical to protect the public health potential of population-level DNA screening. Other challenges include training of the medical workforce and accessibility of downstream health services, including genetic counselling, surveillance, interventions and elective procedures (eg, colonoscopy, prophylactic surgery) if DNA screening reached population scale. The pilot data will identify gaps and potential areas of concern regarding the development future DNA screening programs.

Our previously published health economic modelling studies of DNA screening for HBOC, Lynch syndrome[20] and familial hypercholesterolaemia[21] provide a platform for the consideration of DNA screening in Australia. Compared with current rates of clinical DNA testing, our modelling estimated that population DNA screening for HBOC and Lynch syndrome in adults aged 18–25 years would prevent 2411 cancers and save 1270 lives. At $200 per test, savings in prevented cancer treatment outweighed DNA screening costs, projecting DNA screening to be cost-saving for the Australian public health system (for cancer genes alone). Our model on DNA screening for familial hypercholesterolaemia genes found similar results.[21] Our future modelling will assess the combined benefits and costs of screening for familial cancer genes and familial hypercholesterolaemia genes concurrently in the same test.

The DNA Screen pilot study will enable an evidence-based assessment of population-level adult DNA screening in Australia for the first time. This could help position Australia to become the first nation to offer adult population DNA screening through a public health care system. By purposefully limiting screening to only medically actionable conditions that meet certain evidence thresholds, the study takes a conservative approach. If additional conditions meet these thresholds in the future, then the approach could be expanded. Potential benefits must be balanced against the ethical, societal and implementation challenges.

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