Combined population genomic screening for three high-risk conditions in Australia: a modelling study


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Summary

Background No previous health-economic evaluation has assessed the impact and cost-effectiveness of offering combined adult population genomic screening for multiple high-risk conditions in a national public healthcare system.

Methods This modeling study assessed the impact of offering combined genomic screening for hereditary breast and ovarian cancer, Lynch syndrome and familial hypercholesterolaemia to all young adults in Australia, compared with the current practice of clinical criteria-based testing for each condition separately. The intervention of genomic screening, assumed as an up-front single cost in the first annual model cycle, would detect pathogenic variants in seven high-risk genes. The simulated population was 18–40 year-olds (8,324,242 individuals), modelling per-sample test costs ranging AUD$100–$1200 (base-case AUD$200) from the year 2023 onwards with testing uptake of 50%. Interventions for identified high-risk variant carriers follow current Australian guidelines, modelling imperfect uptake and adherence. Outcome measures were morbidity and mortality due to cancer (breast, ovarian, colorectal and endometrial) and coronary heart disease (CHD) over a lifetime horizon, from healthcare-system and societal perspectives. Outcomes included quality-adjusted life years (QALYs) and incremental cost-effectiveness ratio (ICER), discounted 5% annually (with 3% discounting in scenario analysis).

Findings Over the population lifetime (to age 80 years), the model estimated that genomic screening per-100,000 individuals would lead to 747 QALYs gained by preventing 63 cancers, 31 CHD cases and 97 deaths. In the total model population, this would translate to 31,094 QALYs gained by preventing 2612 cancers, 542 non-fatal CHD events and 4047 total deaths. At AUD$200 per-test, genomic screening would require an investment of AUD$332 million for screening of 50% of the population. Our findings suggest that this intervention would be cost-effective from a healthcare-system perspective, yielding an ICER of AUD$23,926 (~£12,050/€14,110/US$15,345) per QALY gained over the status quo. In scenario analysis with 3% discounting, an ICER of AUD$4758/QALY was obtained. Sensitivity analysis for the base case indicated that combined genomic screening would be cost-effective under 70% of simulations, cost-saving under 25% and not cost-effective under 5%. Threshold analysis showed that genomic screening would be cost-effective under the AUD$50,000/QALY willingness-to-pay threshold at per-test costs up to AUD$325 (~£164/€192/US$208).

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Interpretation Our findings suggest that offering combined genomic screening for high-risk conditions to young adults would be cost-effective in the Australian public healthcare system, at currently realistic testing costs. Other matters, including psychosocial impacts, ethical and societal issues, and implementation challenges, also need consideration.

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Keywords: Population screening; Cost-effectiveness analysis; Health-economic evaluation; Genomic testing; Public health; Prevention; Genomics

Introduction Adult population genomic screening presents an immediate opportunity for public health, particularly to enable the early detection, diagnosis, early intervention, and prevention of cancer and heart disease caused by high-risk inherited genomic conditions. Around 1 in 75 people (1.3% of the general population) across diverse ancestries carry pathogenic or likely pathogenic germline variants for three high-risk medically actionable conditions designated by the US CDC (hereditary breast and ovarian cancer, Lynch syndrome, familial hypercholesterolaemia). These monogenic conditions have been prioritised by the US Centers for Disease Control and Prevention (CDC) as leading candidates for adult population genomic screening owing to their prevalence, high penetrance of disease-associated genes, and availability of evidence-based risk-management options.

The proven risk-management interventions for these conditions can be lifesaving, especially if made available early. Women identified with HBOC pathogenic variants (hereafter referred to as PVs) including in the BRCA1 and BRCA2 genes can access breast imaging (mammography, MRI and/or ultrasound), risk-reducing bilateral mastectomy (RRBM) and salpingo-oophorectomy (RRSO) to reduce breast and ovarian cancer risk. Due to the serious nature of these interventions and fertility implications, the optimal age to offer genomic screening must be carefully considered. For Lynch syndrome, aspirin use and regular colonoscopy can reduce colorectal cancer risk, and hysterectomy with bilateral salpingo-oophorectomy

Research in context

Evidence before this study Previous cost-effectiveness analyses of adult population genomic screening have mostly focused on single condition screening, rather than a combined approach for multiple conditions. We searched PubMed and MEDLINE for articles published up to May 10th 2023 to identify economic evaluations of population genomic screening, using search terms “population genomic screening”, “population-based genetic testing”, “cost-effectiveness analysis”, “health-economic evaluation” and “modelling study”. The literature review identified 14 studies. However, none had assessed the impact of combined genomic screening in a national public healthcare system, for ‘tier 1’ medically actionable conditions designated by the US CDC (hereditary breast and ovarian cancer, Lynch syndrome, familial hypercholesterolaemia). One study assessed such screening in the US system.

Added value of this study Before this study, there was a knowledge gap regarding the feasibility of offering combined population genomic screening for the above conditions in a national public healthcare system setting, with a lack of evidence to inform policy. This study addresses the knowledge gap by modelling combined population genomic screening for all adults aged 18–40 years in the Australian public healthcare system, demonstrating an improvement in the overall cost-effectiveness of combined population genomic screening, versus the status quo of criteria-based genetic testing or screening for individual conditions separately. The modelling is accompanied by a real-world pilot study in Australia of population genomic screening for the same conditions involving 10,000 adults aged 18–40 years from the general population.

Implications of all the available evidence This modelling study provides evidence to inform screening policy in Australia and other jurisdictions, suggesting that offering combined population genomic screening to young adults would be cost-effective in a national public healthcare system. This comes at a time when various healthcare systems and providers around the world are considering the implementation of adult population genomic screening.
can reduce endometrial and ovarian cancer risk.\(^6\) For FH, statins and other cholesterol-lowering agents can markedly reduce the risk of premature coronary heart disease.\(^{21,26}\)

Despite the availability of these multifaceted effective risk-reducing strategies, detection rates for these inherited conditions in the general population remain very low, largely owing to the narrow eligibility criteria for publicly-funded genetic testing.\(^{27,28}\) In most countries, clinical criteria-based genetic testing for these conditions is restricted to individuals with a previous diagnosis and/or strong family history of disease, and is rarely offered to young, unselected adults. This restrictive approach is known to miss up to 90% of high-risk PV carriers in the general population, representing an unmet need and missed opportunity in preventive healthcare.\(^{15,16,19}\) In the UK, in 2018 it was estimated that only 2.5% of female BRCA1 and BRCA2 PV carriers had been identified, despite over 25 years of clinical genetic testing and cascade screening in affected families.\(^19\) This and similar findings in other countries\(^{4,20}\) indicate that the current criteria-based testing model is ineffective and not maximizing the preventative potential of genomics.

The alternative strategy of criteria-free population genomic screening for these conditions (i.e. offering preventive testing for a limited set of high-risk genes to unselected adults from the general population) has much promise.\(^{21,27,28}\) Previous cost-effectiveness analyses suggest that single-condition genomic screening for HBOC or FH alone may already be cost-effective in countries with a national public healthcare system, including Australia\(^{22,23}\) and the UK.\(^{4,16}\) However, results from the USA\(^{29–31}\) and other countries\(^{26,29–31}\) vary, not always suggesting cost-effectiveness for single-condition screening. Other matters also need consideration, including the psychosocial impact of genomic screening, and the ethical and societal issues. A recent study found combined screening for HBOC, LS and FH in the USA is likely to be cost-effective, if offered to 30 year-olds with low-cost testing (<US$300).\(^{11}\) However, the USA is not supported by a national public healthcare system to deliver such genomic screening across the general population, raising concerns about equity of access. In Australia, by contrast, there is a national public healthcare system with implemented population screening programs available to individuals from the general population, funded by the Australian Government and guided by the national Population-Based Screening Framework. Further, the real-world feasibility of population genomic screening in Australia is being piloted in DNA Screen — a national pilot study offering combined screening for HBOC, LS and FH to 10,000 adults aged 18–40 years from the general population.\(^1\) The feasibility of genomic screening is also being evaluated in the PROTECT-C study in the UK public healthcare system.\(^{10,25}\) In the present modelling study, we assess the cost-effectiveness and impact of offering combined genomic screening for HBOC, LS and FH to all adults aged 18–40 years via the Australian public healthcare system to inform future screening policy.

**Methods**

**Model overview**

We designed three decision analyses in combination with Markov models for five different disease outcomes caused by PVs in high-risk genes associated with HBOC (BRCA1 and BRCA2 genes, breast and ovarian cancer; Model 1); LS (MLH1 and MHS2 genes, colorectal cancer in men; colorectal and endometrial cancer in women; Model 2); and FH (LDLR, APOB and PCSK9 genes, coronary heart disease (CHD), Model 3). The genes PALB2 (HBOC) and MHS6 (LS) were not included in the models because of the lack of age-adjusted risk data published for these genes at the time of analysis. For methodological details of each individual model, including model populations, structures, transition probabilities, health states, interventions and risk-reduction strategies, utilities and costs, see the Supplementary Materials.

We first modelled each condition separately (Models 1–3), with events from each model considered mutually exclusive, then combined all models to generate the final results (Combined Model). Each individual model used decision trees followed by cohort multistate transition models (i.e. a cohort transitions from mutually exclusive health states based on given transition probabilities) to compare the health and economic outcomes of two different testing strategies for identifying PV carriers (Fig. 1). Strategy 1 (comparator: the status quo in Australia of criteria-based genetic testing for each condition separately) that assumed current detection rates for each condition individually are 10% (although real detection rates are likely to be far lower\(^1\)). Strategy 2 (intervention: combined population genomic screening for all three conditions) that assumed a 100% detection rate for PV carriers in the modelled population for the base case (at 50% testing uptake and with 100% test sensitivity or specificity). These parameters were varied in sensitivity analyses. For both strategies, the modelled population for the base-case analysis included all Australians aged 18–40 years. We assumed genomic screening was delivered to the whole participating population during the first annual cycle of the model (rather than delivered over a period of several years).

Using life-table modeling (cohort modelling stratifying the population by age and single year of age and assigning sex- and age-specific probabilities), our analysis captured the estimated morbidity and mortality for high-risk PV carriers in the modelled population, identified using either strategy, over a lifetime horizon up to 80 years of age. We assumed all PV carriers (identified through either strategy) would receive post-test genetic counselling and access to standard-of-care risk management, modifications to smoking and alcohol consumption, and statins to reduce cardiovascular risk. Costs and utilities of all strategies were estimated using a standard Markov model time horizon (50 years) and discounted at 5% per year.
management and ongoing surveillance and interventions, the costs of which were accounted for in the model. Risk-reducing interventions followed current Australian guidelines with assumed uptake rates for individual interventions based on published studies (see Table 1). For individual Markov model schematics, see Fig. 2.

The primary outcome of the model was the combined incremental cost-effectiveness ratio (ICER), which was defined as a cost per quality-adjusted life year (QALY) gained, using a willingness-to-pay (WTP) threshold of AU$50,000/QALY. Secondary outcomes included years of life lived, and the number of detrimental events (i.e. fatal and non-fatal breast cancer, ovarian cancer, colorectal cancer and endometrial cancer; and fatal and non-fatal CHD) averted through the implementation of population genomic screening. The model accounted for participation in current Australian population-based cancer screening programs in the status-quo and intervention arms, based on current eligibility criteria and uptake rates for these programs which begin at older ages (see Table 1). For the base-case analysis, the model adopted a healthcare-system perspective, including a societal perspective in the scenario analysis, with all outcomes discounted by 5% annually per standard practice in Australia (varied to 3% in scenario analysis).

Model population

The model population was based on age- and sex-specific data from the Australian Bureau of Statistics in June 2020 and included all Australians aged 18-40 years in the decision-analysis models (8,324,242 individuals). Of this population, 50% were assumed to uptake genomic screening during the first cycle of the model, resulting in 4,162,121 persons screened from the year 2023 onwards. The population genetic prevalence of each condition (i.e. the proportion of individuals in the general population who carry high-risk PVs for the condition) was estimated based on published studies: HBOC (BRCA1 and BRCA2 PVs) = 0.004 (∼1 in 225), LS (MLH1 and MSH2 PVs) = 0.00086 (∼1 in 1160) and FH (LDLR, PCSK9 and APOB PVs) = 0.004 (∼1 in 250). These values were varied in the sensitivity analyses.

Risk and risk-reducing strategies

For HBOC, we estimated the annualized, age-specific risk of breast or ovarian cancer in female PV carriers, compared with women in the general population. Intensive breast cancer surveillance in detected PV carriers was assumed to follow current guidelines (i.e. an annual MRI and ultrasound from 30 years of age until death) with an assumed uptake of 89% and mortality hazard ratio (HR) of 0.13 with a 95% confidence interval.
### Input parameter | Base-case | Range | Distribution | Source
---|---|---|---|---
**General parameters**
Uptake of population genomic screening | 50% | 25-100% | Log-normal | Assumption
Proportion of pathogenic variant (PV) carriers detected in the status-quo cohort (based on current rates of clinical criteria-based genetic testing) | 10% | ±15% | Log-normal | Assumption
Cost per test in the population genomic screening (intervention) cohort | AU$200 | AU$100-AU$1200 | Gamma | Assumption
Cost per clinical diagnostic genetic test in the status-quo cohort | AU$1200 | Fixed | Fixed | MSAC #73296, #73354, #73352
Cost of clinical diagnostic confirmation testing and post-test genetic counseling | AU$529 | ±25% | Gamma | Assumption
Cost per non-cancer death | AU$3304 | ±25% | Gamma | AR-DRG
Specificity of DNA screening | 100% | 70-100% | Log-normal | Assumption
Sensitivity of DNA screening | 100% | 70-100% | Log-normal | Assumption
Utility weights for the health state “Alive, no disease” | Age- and sex-specific (Table S2.1) | Age and sex-specific | Beta | McCaffrey et al.

### Breast and ovarian cancer (screening for the BRCA1 and BRCA2 genes)
Population prevalence of BRCA1 and BRCA2 pathogenic variants (PV) | 0.004 | 0.004-0.006 | Log-normal | Van Hout et al.
BC incidence, general population | Age-specific (Table S3.3) | ±15% | Log-normal | AIHW
OC incidence, general population | Age-specific (Table S3.3) | ±15% | Log-normal | AIHW
BC incidence in BRCA1 and BRCA2 PV carriers (weighted average) | Age-specific (Table S3.3) | ±15% | Log-normal | Kuchenbaecker et al.
OC incidence in BRCA1 and BRCA2 PV carriers (weighted average) | Age-specific (Table S3.3) | ±15% | Log-normal | Kuchenbaecker et al.
Annual probability of remission for BC | 0.37 | ±15% | Log-normal | AIHW
Annual probability of remission for OC | 0.12 | ±15% | Log-normal | AIHW
% uptake of RRM | 57.9% | ±15% | Log-normal | Marcinkute et al.
Starting age for RRM | 40 years | Fixed | Fixed | Marcinkute et al.
% uptake of RRSO | 78.6% | ±15% | Log-normal | Marcinkute et al.
Average age for RRSO | 45 years | Fixed | Fixed | Marcinkute et al.
BC risk reduction after RRM (HR) | 0.061 | 0.02-0.20 | Beta | Marcinkute et al.
OC risk reduction after RRSO (HR) | 0.21 | 0.12-0.39 | Beta | Domscheck et al.
CHD risk increase after RRSO (HR) | 1.03 | 1.00-1.06 | Log-normal | Mytton et al.
BreastScreen uptake (standard of care breast cancer screening program) | 55% | ±15% | Log-normal | AIHW
Starting age for BreastScreen | 50 years | Fixed | Fixed | AIHW
BC intensive screening uptake (for detected PV carriers only) | 89% | 81-100% | Log-normal | Rowley et al.
Starting age of BC intensive screening | 30 | Fixed | Fixed | EviQ guidelines
Mortality reduction in BC from standard screening (RR) | 0.75 | 0.69-0.81 | Beta | Myers et al.
Mortality reduction in BC from intensive screening (RR) | 0.13 | 0.03-0.53 | Beta | Evans et al.
Cost per MRI | AU$690 | ±25% | Gamma | AR-DRG
Cost per mammogram | AU$92 | ±25% | Gamma | MSAC #53903
Cost per RRM (with breast reconstruction) | AU$15,886 | ±25% | Gamma | AR-DRG
Cost per RRSO | AU$8621 | ±25% | Gamma | AR-DRG
Cost per BC case in the initial phase (first year) | AU$38,253 | ±25% | Gamma | Goldsbury et al.
Cost per BC case in the continuing phase (annually) | AU$4222 | ±25% | Gamma | Goldsbury et al.
Cost per fatal BC case | AU$40,522 | ±25% | Gamma | Goldsbury et al.
Cost per OC case in the initial phase (first year) | AU$38,734 | ±25% | Gamma | Goldsbury et al.
Cost per OC case in the continuing phase (annually) | AU$4696 | ±25% | Gamma | Goldsbury et al.
Utility weight BC in intensive screening (adjusted for cancer stages at the time of diagnosis) | 0.85 | ±15% (SD) | Beta | Rautalin et al.
Utility weight BC in standard screening (adjusted for cancer stages at the time of diagnosis) | 0.83 | ±15% (SD) | Beta | Rautalin et al.
Utility weight OC | 0.69 | ±16% (SD) | Beta | Al-Dakkak et al. & Pickard et al.
Utility weight post-BC health state | 0.87 | ±16% (SD) | Beta | Pickard et al.
Utility weight post-OC health state | 0.77 | ±16% (SD) | Beta | Pickard et al.
Utility RRM | 0.88 | ±22% (SD) | Beta | Grann et al.
Utility RRSO | 0.95 | ±10% (SD) | Beta | Grann et al.

(Table 1 continues on next page)
### Model inputs for the base case, distributions and data sources.

#### Endometrial and colorectal cancer (screening for the MLH1 and MHS2 genes)

<table>
<thead>
<tr>
<th>Input parameter</th>
<th>Base-case</th>
<th>Range</th>
<th>Distribution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population prevalence of MLH1 and MHS2 pathogenic variants</td>
<td>0.00086</td>
<td>±15%</td>
<td>Log-normal</td>
<td>Win et al. 5</td>
</tr>
<tr>
<td>CRC incidence, general population</td>
<td>Age- and sex-specific (Table S4.1)</td>
<td>±15%</td>
<td>Log-normal</td>
<td>AIHW 47</td>
</tr>
<tr>
<td>EC incidence, general population</td>
<td>Age- and sex-specific (Table S4.2)</td>
<td>±15%</td>
<td>Log-normal</td>
<td>AIHW 47</td>
</tr>
<tr>
<td>CRC incidence, MLH1 and MHS2 PV carriers</td>
<td>Age- and sex-specific (Table S4.3)</td>
<td>±15%</td>
<td>Log-normal</td>
<td>Jenkins et al. 69</td>
</tr>
<tr>
<td>EC incidence, MLH2 and MHS2 PV carriers (annual)</td>
<td>0.007</td>
<td>±15%</td>
<td>Log-normal</td>
<td>Lynch Syndrome Australia 49</td>
</tr>
<tr>
<td>% uptake of RRH</td>
<td>71%</td>
<td>±15%</td>
<td>Log-normal</td>
<td>Meier et al. 50</td>
</tr>
<tr>
<td>EC risk reduction after RRH</td>
<td>0.00</td>
<td>Fixed</td>
<td>Fixed</td>
<td>Schmeler et al. 51</td>
</tr>
<tr>
<td>Average age for RRH in MLH1 and MSH2 PV carriers</td>
<td>40 years</td>
<td>–</td>
<td>Fixed</td>
<td>Meier et al. 50</td>
</tr>
<tr>
<td>CRC incidence risk reduction by annual colonoscopy</td>
<td>0.85</td>
<td>±15%</td>
<td>Beta</td>
<td>Cancer Council Australia 52</td>
</tr>
<tr>
<td>CRC mortality risk reduction by annual colonoscopy</td>
<td>0.85</td>
<td>±15%</td>
<td>Beta</td>
<td>Cancer Council Australia 52</td>
</tr>
<tr>
<td>% uptake annual colonoscopy in detected PV carriers</td>
<td>87%</td>
<td>75-100%</td>
<td>Log-normal</td>
<td>Meier et al. 50</td>
</tr>
<tr>
<td>Starting age on annual colonoscopy in detected PV carriers</td>
<td>25 years</td>
<td>20-30 years</td>
<td>Fixed</td>
<td>Australian Government Department of Health 53</td>
</tr>
<tr>
<td>iFOBT-based screening starting age (undetected PV carriers)</td>
<td>50 years</td>
<td>45-55</td>
<td>Fixed</td>
<td>Cancer Council Australia 52</td>
</tr>
<tr>
<td>iFOBT-based screening uptake, males</td>
<td>42%</td>
<td>±15%</td>
<td>Log-normal</td>
<td>Cancer Council Australia 52</td>
</tr>
<tr>
<td>iFOBT-based screening uptake, females</td>
<td>45%</td>
<td>±15%</td>
<td>Log-normal</td>
<td>Cancer Council Australia 52</td>
</tr>
<tr>
<td>CRC risk reduction by chemoprevention (daily low-dose aspirin) (RR)</td>
<td>0.65</td>
<td>0.43-0.97</td>
<td>Beta</td>
<td>Burn et al. 14</td>
</tr>
<tr>
<td>Starting age for chemoprevention in detected PV carriers</td>
<td>25 years</td>
<td>20-30</td>
<td>Fixed</td>
<td>Australian Government Department of Health 53</td>
</tr>
<tr>
<td>% uptake of chemoprevention in detected PV carriers</td>
<td>87%</td>
<td>±15%</td>
<td>Log-normal</td>
<td>Meier et al. 50</td>
</tr>
<tr>
<td>Risk of gastrointestinal bleeding with aspirin</td>
<td>1.15</td>
<td>1.11-1.20</td>
<td>Log-normal</td>
<td>Shami et al. 53</td>
</tr>
<tr>
<td>iFOBT costs (biennial)</td>
<td>AU$40</td>
<td>±25%</td>
<td>Gamma</td>
<td>Australian Government Department of Health 53</td>
</tr>
<tr>
<td>Colonoscopy cost (annual or after positive iFOBT test)</td>
<td>AU$1300</td>
<td>±25%</td>
<td>Gamma</td>
<td>Australian Government Department of Health 53</td>
</tr>
<tr>
<td>Low-dose aspirin (annual costs)</td>
<td>AU$139</td>
<td>±25%</td>
<td>Gamma</td>
<td>PBS 41</td>
</tr>
<tr>
<td>Cost per CRC case in the initial phase (first year) (adjusted for disease stage at diagnosis depending on surveillance type)</td>
<td>AU$46,423-44,386</td>
<td>±25%</td>
<td>Gamma</td>
<td>Goldsbury et al. 42 and Kastrinos et al. 56</td>
</tr>
<tr>
<td>Cost per CRC case in the continuing phase (annually)</td>
<td>AU$5998 ±4400</td>
<td>±25%</td>
<td>Gamma</td>
<td>Goldsbury et al. 42</td>
</tr>
<tr>
<td>Cost per EC case in the initial phase (first year)</td>
<td>AU$30;638</td>
<td>±25%</td>
<td>Gamma</td>
<td>Goldsbury et al. 42</td>
</tr>
<tr>
<td>Cost per EC case in the continuing phase (annually)</td>
<td>AU$4773</td>
<td>±25%</td>
<td>Gamma</td>
<td>Goldsbury et al. 42</td>
</tr>
<tr>
<td>Cost per fatal cancer case</td>
<td>AU$62,205</td>
<td>±25%</td>
<td>Gamma</td>
<td>Goldsbury et al. 42</td>
</tr>
<tr>
<td>Cost of hysterectomy</td>
<td>AU$12,124</td>
<td>±25%</td>
<td>Gamma</td>
<td>Lynch Syndrome Australia 19</td>
</tr>
<tr>
<td>Cost per gastrointestinal bleeding hospitalisation</td>
<td>AU$60,769</td>
<td>±25%</td>
<td>Gamma</td>
<td>Roberts et al. 57</td>
</tr>
<tr>
<td>Utility weight CRC</td>
<td>0.76</td>
<td>0.699-0.823</td>
<td>Beta</td>
<td>Farlikka et al. 58</td>
</tr>
<tr>
<td>Utility weight post-CRC health state</td>
<td>0.85</td>
<td>±16% (SD)</td>
<td>Beta</td>
<td>Mulder et al. 59</td>
</tr>
<tr>
<td>Utility weight EC</td>
<td>0.83</td>
<td>±0.02 (SE)</td>
<td>Beta</td>
<td>Ferguson et al. 60</td>
</tr>
<tr>
<td>Utility weight post-EC health state</td>
<td>0.88</td>
<td>±0.02 (SE)</td>
<td>Beta</td>
<td>Ferguson et al. 60</td>
</tr>
</tbody>
</table>

#### Familial hypercholesterolemia (FH) (screening for the LDLR, APOB and PCSK9 genes)

<table>
<thead>
<tr>
<th>Input parameter</th>
<th>Base-case</th>
<th>Range</th>
<th>Distribution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population prevalence of LDLR, APOB and PCSK9 pathogenic variants (PV)</td>
<td>0.004</td>
<td>0.0029-0.0052</td>
<td>Log-normal</td>
<td>Akioyamen et al. 8</td>
</tr>
<tr>
<td>Risk of first CHD event</td>
<td>Age- and sex-specific</td>
<td>±15%</td>
<td>Log-normal</td>
<td>Versmissen et al. 66</td>
</tr>
<tr>
<td>Proportion of fatal CHD</td>
<td>0.129</td>
<td>±15%</td>
<td>Log-normal</td>
<td>Jorstad et al. 61</td>
</tr>
<tr>
<td>Risk of recurrent CHD</td>
<td>Age- and sex-specific</td>
<td>±15%</td>
<td>Log-normal</td>
<td>Steg et al. 55</td>
</tr>
<tr>
<td>Reduction of CHD risk with statins (HR)</td>
<td>0.24</td>
<td>0.18-0.30</td>
<td>Log-normal</td>
<td>Versmissen et al. 66</td>
</tr>
<tr>
<td>Cost of non-fatal CHD</td>
<td>AU$11,047</td>
<td>±25%</td>
<td>Gamma</td>
<td>AR-DRG 44</td>
</tr>
<tr>
<td>Chronic costs post-CHD (annually)</td>
<td>AU$5620</td>
<td>±25%</td>
<td>Gamma</td>
<td>Cobac et al. 63</td>
</tr>
<tr>
<td>Statin treatment costs (annually)</td>
<td>AU$525</td>
<td>±25%</td>
<td>Gamma</td>
<td>PBS 41</td>
</tr>
<tr>
<td>Statin adherence in individuals with a genetic diagnosis of FH</td>
<td>79%</td>
<td>±15%</td>
<td>Log-normal</td>
<td>Lutrinik et al. 64</td>
</tr>
<tr>
<td>Statin adherence in individuals prescribed statins from the general population (without a genetic diagnosis of FH)</td>
<td>50%</td>
<td>±15%</td>
<td>Log-normal</td>
<td>Talc et al. 55</td>
</tr>
<tr>
<td>Utility weights for “Alive, with CHD*”</td>
<td>0.80</td>
<td>0.57-1.00</td>
<td>Beta</td>
<td>Lewis et al. 66</td>
</tr>
<tr>
<td>Utility weights for an acute CHD event</td>
<td>0.71</td>
<td>0.41-1.00</td>
<td>Beta</td>
<td>Lewis et al. 66</td>
</tr>
</tbody>
</table>

Abbreviations: PV, pathogenic variant; BC, breast cancer; OC, ovarian cancer; RRH, risk-reducing hysterectomy; R50, risk-reducing salpingo-oophorectomy; HR, hazard ratio; CHD, coronary heart disease; MR, magnetic resonance imaging; CRC, colorectal cancer; iFOBT, immunochemical faecal occult blood test; EC, endometrial cancer; RRH, risk-reducing hysterectomy; RR, relative risk; AU$, Australian dollars; SD, standard deviation; SE, standard error; MBS, Medicare Benefits Schedule; MSAC, Medical Services Advisory Committee; AR-DRG, Australian Refined Diagnosis-Related Groups; AIHW, Australian Institute of Health and Welfare; PBS, Pharmaceutical Benefits Scheme. All costs are presented in 2021 AU$. 

Table 1: Model inputs for the base case, distributions and data sources.
interval (CI) of 0.032–0.53). Further risk-reducing strategies included RRBM (assumed uptake of 60% at an age of 40 years; breast cancer HR of 0.061 with a 95% CI of 0.02–0.20) and RRSO (assumed uptake of 78% at an age of 45 years; ovarian cancer HR of 0.21 with a 95% CI of 0.12–0.39). The impacts on cancer-specific mortality and remission were also estimated (see the Supplementary Materials). Routine breast-cancer surveillance was assumed in undetected PV carriers (age of biennial mammograms of 50–74 years; 54% uptake; breast cancer HR of 0.75 with a 95% CI of 0.69–0.81). No ovarian-cancer screening was modelled (no screening options are currently available).

For LS, we estimated outcomes for colorectal cancer in men, and colorectal and endometrial cancer in women. The risk of colorectal cancer in PV carriers versus the general population was estimated using age- and sex-specific hazard ratios, modified by surveillance strategies. The impact of surveillance on remission and mortality risk was modelled. All undetected PV carriers were assumed to have access to standard bowel cancer screening from age 50 years (i.e. biennial immunochemical fecal occult blood test (iFOBT), uptake: 45% for women and 42% for men, with colonoscopy following positive result). Detected high-risk PV carriers were assumed to undergo intensive surveillance (annual colonoscopy, 15% reduction in incidence and mortality) and chemoprevention (daily aspirin, 40% reduction in incidence) from an age of 25 years (accounting for the excess risk of gastrointestinal bleeding due to aspirin). Lifetime rather than annualized risk of endometrial cancer was estimated in female MLH1 and MHS2 PV carriers owing to the lack of age-specific data. Risk-reducing hysterectomy (RRH) was assumed to have a 62% uptake at an age of 45 years in women.

For FH, estimates of age- and sex-specific CHD risk and risk-reducing strategies have been validated and published previously. Briefly, this included annualized risk estimates for incident CHD, risk of recurrent CHD, and risk reduction strategies for CHD using cholesterol-lowering statins (CHD HR of 0.24, 95% CI 0.18–0.30). We assumed statin adherence rates of 79% for individuals following a genetic diagnosis of FH (identified either by population genomic screening or clinical criteria-based genetic testing) and 49.0% for individuals prescribed statins from the general population for any other reason.

Utility scores and costs
Utility scores (values associated with a given health state, with values ranging from 0 to 1) (Table 1) were derived from the literature and originally extracted using the EuroQol 5 dimensions 5 levels questionnaire (EQ-5D-5L). For all models, age- and sex-specific utility scores for the “disease free” health state were extracted from a cross-sectional Australia-specific study (n = 2900 healthy individuals) measuring quality-of-life scores for the general population. The costs for each specific health state and for all acute events, procedures and adverse events are collated in Table 1 and presented in detail in the Supplementary Materials.

For Strategy 1 (status-quo arm of the model), the cost of clinical-criteria-based genetic testing was set at AU$1200, equivalent to the current reimbursement rate for publicly funded criteria-based-genetic testing of each of these conditions in Australia (Medicare Benefits Schedule Items 73,296 [HBOC], 73,354 [LS] and 73,352 [FH]). In the intervention arm (Strategy 2, population genomic screening), we assumed a cost per test of AU$200 (~£115/€130/US$140) for the
combined testing of all three conditions. This was the cost that was varied in the scenario analyses (AU$50–AU$1200).

The cost per test of AU$200 was selected based on the current approximate cost of delivering the same type of testing (for the same genes) to a pilot study population of 10,000 adults in Australia, in a research setting.12 The cost includes postal saliva DNA collection nationwide, laboratory sample processing and DNA extraction, library preparation, targeted DNA sequencing using a custom panel of high-risk genes, data analysis and sample storage fees in Australia. The gene list used in the model does not include any moderate-risk genes. All acute and chronic costs for each model were derived from published sources. All costs were Australian specific and are presented in 2022 AU$. If costs were derived from previous years, the Australian health price index was used to adjust for inflation. All costs are available in Table 1 and Supplementary Materials.

Scenario and sensitivity analyses
We performed scenario and sensitivity analyses to test the effect of varying key input parameters and the internal reliability of the models. In the scenario analyses, we tested variations in: a) the discount rate (0–6%); b) the age range of the selected population (18–40, 18–50 and 25–50 years); and d) adopting a societal perspective, including productivity losses using the human-capital approach (estimating indirect costs due to reduced productivity and accounting for foregone future earnings).13 Scenario analyses for each separate model are presented in the Supplementary Materials.

We performed one-way sensitivity analyses to determine the key drivers of cost-effectiveness in each model separately, using the upper and lower range presented for each input parameter in Table 1. A probabilistic sensitivity analysis was also run using 10,000 Monte Carlo simulations, using the distributions of each input parameter rather than the point estimates. Distributions for each parameter are also presented in Table 1. The model was built using Microsoft Excel (2016) and sensitivity analyses were performed with @Risk (version 7.6) and R software (4.3.1). This study followed the 2022 Consolidated Health Economic Evaluation Reporting Standards (Appendix 6, Supplementary Materials).

Ethics
This health-economic evaluation is part of the DNA Screen project, approved by the Alfred Hospital Research Ethics Committee (Project #597/21). Participant informed consent was not required for this study type.

Role of the funding source
Funders had no role in the study design; collection, analysis, and interpretation of data; writing of the report; or decision to submit for publication. All authors confirm that they had full access to all the data in the study and accept responsibility for the decision to submit for publication.

Results
Base-case analysis
Over the lifetime of the modelled population and compared with the status quo of criteria-based genetic testing, the alternative strategy of combined population genomic screening for the three high-risk conditions (followed by subsequent interventions) was estimated to prevent 2612 cancer cases (1140 breast, 950 ovarian, 451 colorectal and 71 endometrial), 542 non-fatal CHD events and 4047 deaths due to cancer and/or CHD (Table 2). Per-100,000 individuals screened, this would result in the prevention of 63 cancer cases, 31 CHD cases and 97 deaths. Offering genomic screening and subsequent interventions to the modelled population would lead to 20,553 extra years of life lived and 31,094 extra QALYs, compared to the status quo. Per-100,000 individuals screened, this would result in 494 extra years of life lived and 747 extra QALYs.

With an assumed per-test cost of AU$200 for combined genomic screening, the cost of offering testing alone to the modelled population, assuming a 50% testing uptake rate, would be AU$832 million above current estimated expenditure on genetic testing in Australia (assumed as an up-front single cost in the first annual cycle of the model). Offering genomic screening would then incur a further AU$282 million in additional direct healthcare costs related to ongoing surveillance and risk-management of identified PV carriers (itemized in Table 2). This includes an assumed AU$539 per PV carrier for clinical confirmatory testing and post-test genetic counseling.

However, the resulting savings through early detection or prevention of cancer and heart disease achieved by genomic screening would exceed AU$394 million, including AU$198.97 million saved on chronic CHD costs, AU$72.99 million saved on cancer treatments, and AU$15.54 million of savings related to death. Given the total estimated net cost of genomic screening to the modelled population (AU$825.54 million), this translates into a cost-effective ICER in the Australian healthcare system of AU$36,252/YLL and AU$23,963/QALY gained (well below the established willingness-to-pay [WTP] threshold of AU$50,000/QALY gained) (Table 3). Threshold analysis indicated that cost-effectiveness would be maintained under this threshold for per-test costs up to AU$325.

Scenario analyses
In the scenario analyses (Table 3), we investigated the impact of modifying the age range of individuals to whom population genomic screening would be offered.
from 18–40 years (base case) to 18–50 years and 25–50 years. The ICERs for these age ranges (compared with the status-quo arm of no genomic screening) were also cost-effective well under the WTP-threshold, with an ICER of $21,299/QALY for the 18–50-year-old group and $28,317/QALY for the 25–50-year-old group. When the different age groups were compared against the base case, the base case (i.e. genomic screening for 18–40 years old) resulted in the dominant strategy, yielding higher costs and higher QALYs gained (Table 4).

When considering each model independently using the base-case settings, we found that offering genomic screening for FH alone was cost-effective (ICER of AU$40,016/QALY), whereas screening for HBOC alone (ICER of AU$382,396/QALY) or LS alone (ICER of AU$136,658/QALY) would not be cost-effective in the same modelled population. For detailed results of the individual models, see the Supplementary Materials).

From a societal perspective, using the human-capital approach and considering productivity costs due to the

<table>
<thead>
<tr>
<th>Total screened population = 4,162,121</th>
<th>Status quo (comparator)</th>
<th>Population genomic screening (intervention)</th>
<th>Difference (intervention versus comparator)</th>
<th>Per 100,000 screened</th>
</tr>
</thead>
<tbody>
<tr>
<td>BC cases</td>
<td>10,405</td>
<td>9265</td>
<td>−1140</td>
<td>−27</td>
</tr>
<tr>
<td>OC cases</td>
<td>3712</td>
<td>2762</td>
<td>−950</td>
<td>−23</td>
</tr>
<tr>
<td>CRC cases</td>
<td>4438</td>
<td>3987</td>
<td>−451</td>
<td>−11</td>
</tr>
<tr>
<td>EC cases</td>
<td>629</td>
<td>557</td>
<td>−71</td>
<td>−2</td>
</tr>
<tr>
<td>All cancer cases</td>
<td>39,184</td>
<td>16,571</td>
<td>−2612</td>
<td>−63</td>
</tr>
<tr>
<td>Cancer deaths</td>
<td>3631</td>
<td>2691</td>
<td>−939</td>
<td>−23</td>
</tr>
<tr>
<td>Non-fatal CHD cases</td>
<td>40,213</td>
<td>39,071</td>
<td>−1140</td>
<td>−13</td>
</tr>
<tr>
<td>CHD deaths</td>
<td>17,931</td>
<td>17,172</td>
<td>−759</td>
<td>−18</td>
</tr>
<tr>
<td>All CHD cases</td>
<td>58,144</td>
<td>56,843</td>
<td>−1300</td>
<td>−31</td>
</tr>
<tr>
<td>Total deaths (CHD and cancer)</td>
<td>21,561</td>
<td>17,514</td>
<td>−4047</td>
<td>−97</td>
</tr>
<tr>
<td>YLL</td>
<td>1,178,463</td>
<td>1,199,778</td>
<td>20,553</td>
<td>494</td>
</tr>
<tr>
<td>QALYs</td>
<td>1,002,194</td>
<td>1,034,265</td>
<td>31,094</td>
<td>749</td>
</tr>
</tbody>
</table>

Genetic testing costs                $6,934,303                  $825,547,447                           $419,727
Genetic counseling costs             $3,130,249                  $17,469,546                             $629,260
Acute CHD costs                     $249,770,917               $26,190,573                              $4,780,513
Chronic CHD costs                   $1,492,933,141             $198,970,749                             $576,590
Lipid-lowering treatment costs      $70,090,603                $23,998,362                              $1,317,209
Risk reduction surgeries costs      $13,705,954                $54,823,818                              $1,342,019
High-risk surveillance for BC       $16,170,573                $55,856,472                              $1,922,736
High-risk surveillance for CRC      $15,981,044                $80,026,611                              $2,509
Gastrointestinal bleeding costs     $269,587                   $1,078,346                                $1,753,892
Cancer treatment costs              $461,239,708               $372,999,103                             $173,491
Death costs                         $188,069,538               $15,545,128                              $419,727
Healthcare costs                    $2,411,361,314            $1,078,346                                $1,317,209
Total costs (with PGS)              $745,095,048               $17,901,811                               $494
ICER (cost)/YLL                     $36,252                    $23,963
ICER (cost)/QALY                     $56,252                   $23,963

Abbreviations: CHD, coronary heart disease; BC, breast cancer; OC, ovarian cancer; CRC, colorectal cancer; EC, endometrial cancer; YLL, years of life lived; QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio. For detailed results in each individual model, see the Supplementary Materials. aIncludes all healthcare costs except the cost of PGS.

Table 2: Main health, economic results and cost-effectiveness results for the base-case analysis from the combined model.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>ICER (AUS/YLL)</th>
<th>ICER (AUS/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>$36,252</td>
<td>$23,963</td>
</tr>
<tr>
<td>Increasing population genomic screening uptake to 75%</td>
<td>$46,871</td>
<td>$31,360</td>
</tr>
<tr>
<td>(base case 50%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual discount rate 0% (base case 5%)</td>
<td>$3972</td>
<td>$1263</td>
</tr>
<tr>
<td>Annual discount rate 3% (base case 5%)</td>
<td>$7401</td>
<td>$4758</td>
</tr>
<tr>
<td>Cost per test AU$50 (base case AU$200)</td>
<td>$5874</td>
<td>$3883</td>
</tr>
<tr>
<td>Cost per test AU$100 (base case AU$200)</td>
<td>$16,000</td>
<td>$10,576</td>
</tr>
<tr>
<td>Cost per test AU$500 (base case AU$200)</td>
<td>$97,007</td>
<td>$64,123</td>
</tr>
<tr>
<td>Cost per test AU$1200 (base case AU$200)</td>
<td>$238,769</td>
<td>$157,830</td>
</tr>
<tr>
<td>Age range 18–50 years (base case 18–40)</td>
<td>$31,825</td>
<td>$21,299</td>
</tr>
<tr>
<td>Age range 25–50 years (base case 18–40)</td>
<td>$42,175</td>
<td>$28,317</td>
</tr>
<tr>
<td>Societal perspective (including indirect costs using the human-capital approach)</td>
<td>Dominant ⋄</td>
<td>Dominant ⋄</td>
</tr>
</tbody>
</table>

*Dominant ICERs represent cost-saving results.

Abbreviations: ICER, incremental cost-effectiveness ratio; YLL, years of life lived; QALY, quality-adjusted life year.

Table 3: Results from scenario analysis for the combined model.
increased morbidity and mortality in individuals with HBOC/LS/FH variants, at AU$200 per test, the intervention of population genomic screening would be cost saving (dominant ICER individually) versus the status quo (Table 3). Scenario analyses showed that if the per-test cost was increased to AU$325 per test, genomic screening would still be cost-effective below the AU$50,000/QALY WTP threshold. However, at AU$500 per test, the ICER would no longer be cost-effective (AU$64,123/QALY) with 5% annual discounting.

Lowering the discount rate of the base case from 5% to 3% (at AU$200 per test) had a major impact on the model results. The ICER for combined genomic screening using a 3% annual discount rate lowered from AU$23,963/QALY (5% discounting rate, base case) to AU$4758/QALY (3% discounting rate, scenario analysis). The 3% discounting rate is the most common rate in jurisdictions other than Australia.

### Sensitivity analyses

Results from a one-way sensitivity analysis (Fig. 3) indicated that all input variations in the base case model (assuming AU$200 per test and combined genomic screening for HBOC/LS/FH) led to an estimated ICER under the cost-effectiveness threshold of AU$50,000/QALY gained. Results from probabilistic sensitivity analysis (Fig. 4) demonstrate the improved cost-effectiveness of combined screening, and indicate that in the base-case analysis (AU$200 per test), combined genomic screening would be cost-effective under 70% of simulations, cost-saving under 25% and not cost-effective under 5% (Fig. 4b).

### Discussion

Our model of combined population genomic screening estimated the prevention of thousands of cancers, heart disease cases and deaths in high-risk individuals aged 18–40 years in the general Australian population. Currently, the vast majority of these high-risk individuals are not being identified by the status quo of clinical criteria-based genetic testing. Our model indicated that the intervention of genomic screening, if offered at AU$200 per test, would be cost-effective in the Australian public healthcare system, yielding an ICER of AU$23,963/QALY under the status quo. In scenario analysis using a 3% discounting rate, the ICER reduced further to AU$4758/QALY. Currently in
Australia, clinical genetic testing for either HBOC, LS or FH individually (for patients who meet strict eligibility criteria) is reimbursed at a fee of AU$1200 per test.\textsuperscript{33} Threshold analysis indicated that the alternative detection strategy of population genomic screening for these conditions would need to be deliverable at AU$325 per test (or lower) to be considered cost-effective in the Australian public healthcare system, below the AU$50,000 willingness-to-pay (WTP) threshold with 5\% discounting. Internationally, clinical-grade tests from commercial providers are now available for AU$280–AU$450, and other studies have also modelled genomic screening using a US$200 per-test cost,\textsuperscript{27–29} indicating these price ranges are now achievable. In the future, prices may fall further, making the prospect of genomic screening even more cost-effective and feasible.

Previous modeling studies of population genomic screening for individual conditions (e.g. HBOC and FH) have indicated potential cost-effectiveness in countries with a national public healthcare system, including Australia\textsuperscript{23,24} and the UK.\textsuperscript{25,26} However, our study suggests there would be an improvement in the overall cost-effectiveness and efficiency of genomic screening if offered in a combined fashion for multiple conditions together, for example screening for hereditary cancer predisposition syndromes and FH concurrently (assuming the per-test cost can be maintained, which is possible with current sequencing technology). This combined approach to genomic screening is supported by recent modelling by Guzauskas et al. in the US, demonstrating that cost-effectiveness is improved by combined screening of HBOC, LS and FH in individuals aged 30 years in a US health system.\textsuperscript{31}

There are several important differences between our study and that of Guzauskas et al. The two studies are based on fundamentally different healthcare systems in different countries (Australia versus the US), which vary by structure, reimbursement methods, costs and participation rates. In particular, the amount of baseline screening, detection and participation in these healthcare systems (as represented in standard-of-care model arms) vary greatly. The two studies used different source of inputs and model parameters and settings. The model of Guzauskas et al. includes cascade testing in the final ICER calculation, whereas our model does not. This is likely to have a considerable bearing on overall cost-effectiveness, given that, on average, cascade testing can identify up to three more high-risk individuals per family identified.\textsuperscript{20} Guzauskas et al. applied a 3\% discounting rate (versus 5\% in our study) and modelled testing at US$250 per-sample (~AU$390) versus our figure of AU$200. Guzauskas et al. also modelled genomic screening at a single timepoint (cohort of 30-year-olds) in the base-case, rather than an age-range (e.g. 18–40-year-olds). The WTP used in Australian studies (AU$50,000 or ~US$38,750 per QALY) is considerably lower than the US WTP of US$100,000 (or ~AU$147,000) per QALY. These and other differences make the direct comparison of results from the two studies complicated. Ultimately, both studies estimated that offering population genomic screening in two different healthcare systems for the same three conditions would be cost-effective for young adults (ICERs of US$68,600/QALY versus AU$23,580/QALY for the respective base-cases).

In our model of the Australian national public healthcare system, we observed a higher proportional impact of FH and cardiovascular prevention (relative to cancer prevention) than in the model of Guzauskas et al. Although there are several possible explanations for this, our hypothesis is that baseline cancer screening and prevention in Australia (in the status-quo arm) may be
higher than the US, largely due to the established and implemented national population-based cancer screening programs in Australia (e.g., breast cancer and bowel cancer screening, available to all adults aged 50–74 years). This baseline difference in cancer screening and prevention in Australia may mean that the incremental impact of adding population genomic screening may be lower in Australia than in the US for cancer, relative to the status quo.

In Australia, there is a national public healthcare system with a proven ability to deliver population-based screening programs that are funded by the Australian Government and guided by the established national Population-Based Screening Framework. Under these circumstances, the prospect of implementing a national DNA-based population screening program is feasible in Australia. The ICER for the base case of our model (AUD$23,963/QALY-gained or AUD$36,252/YLL) suggests that the cost-effectiveness of offering a population genomic screening program to 18–40 year-olds would be comparable to existing population-based screening programs in Australia. For example, recent modeling of existing Australian population-based cancer screening programs estimated ICERs ranging from AUD$3380 to AUD$65,065 per life-year saved (LYS, a comparable measure to YLL). The national breast screening program (BreastScreen Australia) offers biennial mammography to women aged 65–69 years (ICER of AUD$40,279–65,065/LYS). The National Cervical Screening Program offers biennial human papillomavirus testing for 25–74-year-old women (ICER of AUD$16,632/LYS). The National Bowel Cancer Screening Program offers biennial fecal occult blood testing to 50–75-year-old men and women (ICER of AUD$3380/LYS). Thus, offering combined genomic screening for the conditions modelled in our analyses (ICER of AUD$31,196/YLL) would fit within the acceptable cost-effectiveness range of these programs. From a societal perspective, considering the broader economic impacts on workforce productivity and other factors, our modelling suggested that genomic screening would be cost saving (i.e. dominant strategy) in the Australian system. This result is supported by other cost-effectiveness analyses of genomic screening in other western health systems, using a societal perspective for reimbursement policies.

The optimal age range to offer genomic screening must be considered carefully by policy makers. Other studies have shown that offering genomic screening to all women aged ≥18 years (with no upper age limit) for the BRCA1 and BRCA2 genes would be cost-effective. These studies are supported by evidence of feasibility, acceptability and satisfaction among research participants. Factors beyond the age-range of genomic screening also need to be considered in the overall assessment. For example, the allocative efficiency and maximization of consumer benefits that are not financially quantifiable must be considered. This includes implications for reproductive decision making, variability in uptake rates, and differing views of “medical actionability” among different societal and age groups. The potential anxiety experienced by very young adults when receiving cancer risk information between the ages of 18 and 25 years (when high-risk surveillance may not commence until the age of 30 years), must be balanced against preventive benefits, including reproductive implications. For FH, commencement of cholesterol-lowering treatment is typically recommended directly after a genetic diagnosis, even for children, making early PV detection a priority.

Further ethical and societal issues must be also considered. We highlight the need for more public education and awareness of genomics in society, as well as an appropriate informed-consent framework for population genomic screening to discuss potential benefits and harms, and the need to protect high-risk individuals against genetic discrimination. From a resourcing perspective, providing timely access to downstream clinical care, risk management and genetic counseling services is a major implementation challenge and potential barrier. Further research and piloting are required to understand the full itemization of costs and associated services that would be required to support genomic screening, including programmatic delivery, overheads, genetic counselling, clinical geneticist and other specialist care, and staffing requirements associated with implementing a screening program in a national healthcare system. These costs and services will vary between countries and healthcare systems.

There is no consensus on which conditions (or genes) should be included in population genomic screening. Previous modeling studies have focused on cancer genes and mostly in women. Our model focuses on three high-risk, medically actionable genomic conditions and expands screening to include cardiovascular disease (FH) genes and includes men. Although some guidance on genomic screening is emerging, we included only individual “Tier 1” genomic applications designated by the US CDC. There is an emerging need to develop more evidence-based approaches for the consideration of additional conditions and genes in population genomic screening initiatives, including the possible use of positive predictive value as a more agnostic approach. An extended gene panel for (moderate to high penetration) HBOC genes has been shown to be cost-effective in women in the UK and USA. While acknowledging that other genes and conditions deserve consideration for population screening, we note the inclusion of lower-penetration genes and moderate risk conditions may shift the overall cost-effectiveness. Future modeling may consider this question. Our model assumed variants of uncertain significance (VUS) would not be returned in
population screening. We acknowledge the complexity of returning VUS, and that different approaches are being taken internationally.21,22

Strengths of our study include the detailed modeling and use of annualized age-and sex-adjusted risk data, and Markov models across five different disease outcomes (breast, ovarian, colorectal, endometrial cancer and coronary heart disease) and three genomic conditions. We used model inputs based on published studies and sought expert clinical advice for each disease model. Our modelling is timely due to the recent introduction of the Australian Government-funded DNA Screen national pilot study, which is currently offering population genomic screening to 10,000 represented adults aged 18–40 years in Australia for the same conditions modelled.77 Our findings are therefore of immediate relevance to future Australian health policy considerations and directly comparable to a real-world pilot study of the same target population and demographic.

Limitations of our study include the assumptions made about uptake of genetic screening (50% in the base case) and the sensitivity and specificity of genomic testing (100%). We acknowledge that the uptake of population genomic screening in Australia is untested. We assumed 50% uptake, which is consistent with the uptake of existing population-based screening programs in Australia.78 Our model did not include the PALB2 and MSH6 genes, or moderate-risk HBOC genes, which are often included on expanded gene panels.25 We excluded the PMS2 gene (for Lynch syndrome) from both our model and the DNA Screen pilot study, as the gene was deemed to be of insufficient penetrance to warrant inclusion in population screening. Our study did not assess public perceptions and preferences, patient-reported outcomes or experience measures, or explore issues related to equity and access. Whilst our model accounted for some additional costs incurred by population genomic screening, such as clinical confirmation testing and post-test genetic counseling (AUS$19), it is likely that further hidden costs exist within the system and have not been accounted for, including potential costs related to workforce expansion, public education, recruitment, programmatic staffing and laboratory overheads. We acknowledge there is uncertainty around the uptake rates, adherence and compliance to recommended interventions for high-risk individuals once identified, and potential hidden costs for downstream clinical services and interventions for these individuals, including complications related to risk-reducing surgeries or colonoscopies. We did not consider in detail how genomic screening would interface with other population screening programs, including the national breast cancer and bowel cancer screening programs in Australia.

For simplicity, our model assumed that genomic screening was offered in the first annual cycle of the model (as an up-front single cost) rather than amortized over the decades required to implement a screening program. The model did not distinguish between early- and late-stage cancers, considering all to be equally invasive with an averaged treatment cost.37 We assumed equivalence of future disease risk (i.e. gene penetrance) in PV carriers ascertained either clinically6,7,16 or by population screening. We acknowledge there may be differences in penetrance based on ascertainment method, genetic diversity or ancestry, with gaps remaining in evidence. Although early gene-penetrance estimates from the general population may be lower than in clinically-ascertained cohorts36,81 it is likely that for the high-risk genes included in our model, there will still be sufficiently high positive predictive value upon PV detection to warrant intervention and risk management, even with reduced penetrance. For the purposes of our model, we used penetrance estimates only from highly-cited epidemiological studies6,7,16 and applied ±15% confidence ranges to all risk estimates to address this uncertainty.

There is an emerging public health opportunity to offer adult population genomic screening to improve the early detection and prevention of cancer and heart disease caused by high-risk inherited monogenic conditions. Our modelling demonstrates a marked improvement in the overall cost-effectiveness of offering population genomic screening in a combined fashion for multiple conditions together, versus criteria-based clinical genetic testing or screening for individual conditions. The model structure can be applied to other healthcare systems, making our findings relevant for international jurisdictions, especially countries with national public healthcare systems capable of delivering nation-wide population screening programs.

Contributors
PL conceived the study. PL, CM, JT and ZA designed the study, reviewed the literature, collected data, interpreted results and wrote the manuscript. CM led the modelling analyses, with supervision from ZA, who together generated results, wrote code and developed figures. CM and ZA verified the underlying data. AB, KN, YJK, MM, RM, KC and JJM provided epidemiological and methodological oversight. Clinical expertise was provided by RCG, RM, GFW, PJ, IW and JM. All co-authors provided critique and/or review of the manuscript. PL and ZA are responsible for the overall content as guarantors. All authors confirm that they had full access to all the data in the study and accept responsibility for the decision to submit for publication.

Data sharing statement
Model available upon request from the corresponding author.

Declaration of interests
RM. declares advisory board membership from Astrazeneca/MSD/EGl/GSK. RCG. has received compensation for advising Allelica, Fabric, GenomeWeb, Genomic Life and Verily; and is a co-founder of Genome Medical and Nurture Genomics. KC. is co-Principal Investigator (PI) of an investigator-initiated trial of cervical screening, Compass, run by the Australian Centre for Prevention of Cervical Cancer (ACPCc), which is a government-funded not-for-profit charity; the ACPCc has received equipment and a funding contribution from Roche Molecular Diagnostics, and operational support from the Australian Government. KC. is also co-PI on a major investigator-initiated...
implementation program Elimination of Cervical Cancer in the Western Pacific (ECCWP) receives support from the Minderhoed Foundation and equipment donations from Cepheid Inc. No other authors declare competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102297.

References

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