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ARTICLE

Economic evaluation of population-based, expanded reproductive carrier screening for genetic diseases in Australia

Deborah Schofield[1], Evelyn Lee[1,*], Jayamala Parmar[1], Simon Kelly[2], Matthew Hobbs[3], Nigel Laing[4], Jan Mumford[5], Rupendra Shrestha[1]

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ABSTRACT

Purpose: This study aimed to evaluate the cost effectiveness of population-based, expanded reproductive carrier screening (RCS) for a 300 recessive gene panel from health service and societal perspectives.

Methods: A microsimulation model (PreConMod) was developed using 2016 Australian Census data as the base population. Epidemiologic, health, and indirect cost data were based on literature review. The study assessed the incremental cost effectiveness ratio of expanded RCS compared with (1) no population screening and (2) 3-condition screening for cystic fibrosis, spinal muscular atrophy, and fragile X syndrome in a single birth cohort. Averted affected births and health service savings with expanded RCS were projected to year 2061. Both one-way and probability sensitivity analyses were conducted to assess the uncertainty of the parameter inputs.

Results: Expanded RCS was cost saving compared with no population screening and cost effective compared with the 3-condition screening (incremental cost effectiveness ratio of Australian dollar [AUD] 6287 per quality-adjusted life year gained) at an uptake rate of 50% for RCS, 59% for in vitro fertilization and preimplantation genetic testing, 90% for prenatal diagnosis testing, and 50% for elective termination of affected pregnancies and a cost of AUD595 per couple screened. Our model predicts that expanded RCS would avert one-third of affected births in a single birth cohort and reduce lifetime health service spending by AUD632.0 million. Expanded RCS was estimated to be cost saving from the societal perspective.

Conclusion: Expanded RCS is cost effective from health service and societal perspectives. Expanded RCS is projected to avert significantly more affected births and result in health service saving beyond those expected from 3-condition screening or no population screening.

Deborah Schofield and Evelyn Lee are co–first authors.

*Correspondence and requests for materials should be addressed to Evelyn Lee, GenIMPACT: Centre for Economic Impacts of Genomic Medicine, Macquarie Business School, 4 Eastern Rd, Macquarie University, New South Wales 2109, Australia. *Email address:* evelyn.lee@mq.edu.au

Affiliations are at the end of the document

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Introduction

Mendelian disorders are individually rare but collectively they affect as many as 2% to 5% of all live births, accounting for 20% of deaths in the first year of life and a significant number of pediatric hospital admissions.[1,2] Beyond the neonatal period, it is estimated that 1 in 3 children affected by genetic conditions will die by age 5 years and many will have major morbidities that are likely to affect their long-term prognosis.[3,4] Reproductive carrier screening (RCS) of prospective parents has been shown to be effective in identifying gene variants associated with heritable disorders.[5,6] The intent of carrier screening is to identify asymptomatic individuals heterozygous for likely pathogenic or pathogenic variants that cause autosomal or X-linked recessive conditions before or during the early stage of pregnancy to facilitate informed reproductive decisions, such as preimplantation genetic testing (PGT) during in vitro fertilization (IVF) treatment, the use of donor gametes or refraining from conceiving to avoid passing on such disorders to their offspring, or termination of an affected fetus.

Traditionally, carrier screening is targeted toward individuals with a known family history of a specific genetic disorder or those from specific at-risk ethnic groups.[7] Several studies have shown that this ethnicity-based screening approach for autosomal recessive conditions is effective in reducing disease prevalence, resulting in fewer children born with genetic disorders in the ethnic group.[6,8] However, there exists concerns that such an approach to carrier screening could miss many at-risk individuals from other ethnic groups or individuals with mixed or unknown ancestry.[9] For example, in a retrospective review of clinical data from an expanded carrier screening test for 108 diseases conducted on 23,453 patients, Lazarin et al[10] found that almost 1 in 4 of the patients (24%) were individuals heterozygous for a pathogenic variant that was not covered by current screening guidelines. These findings were also confirmed in a modeling study on a clinical sample of 346,790 individuals involved in perinatal care where expanded carrier screening identified an additional 9% to 55% pathogenic variants depending on ethnic and racial background compared with an ethnicity-based screening approach.[11]

More recent advances in technology and genetic sequencing have enabled the development of multiplex panels, which efficiently test for a larger number of conditions at an affordable cost.[12] This development has also led to increasing commercial offering of expanded carrier screening so that individuals who are generally healthy and lack family history for genetic conditions can acquire information about whether they have an increased risk of conceiving an affected child. Recognizing the potential benefits, several organizations, such as the American College of Medical Genetics and Genomics and the American College of Obstetricians and Gynecologists, have supported the widespread offering of expanded carrier screening to couples who are considering pregnancy or are already pregnant, regardless of ethnicity.[5,13] Similarly, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists recommends that information on carrier screening for more common genetic conditions that affect children be offered to women before conception or early in pregnancy as part of patient care.[14]

However, as evidence supporting the benefits of expanded RCS for inheritable recessive disorders grows, cost is an important consideration when determining whether and how expanded RCS initiatives would fit into existing care pathways especially within a publicly funded health care system.[15] The question on whether expanded RCS offered at the population level would provide good value for money given finite health resources remains a subject of extensive debate.[16,17] Previous modeling studies have indicated that RCS is cost effective.[18,19] However, these studies have been limited by their focus on one or a small number of recessive disorders and short-term effect of carrier screening.[18-20] Outcome measures were reported in natural units, such as life years gained, disability-adjusted life years (DALY), and frequency of recurrence (or cases averted), which render comparisons of RCS with other areas of health disease difficult for priority setting and informing resource allocation decisions.[21] Other studies did not model uptake rate for RCS and used a single cost estimate for all downstream interventions (eg, PGT, IVF), which may underestimate cost effectiveness findings.[18,19] A common measure is important to allow health gains associated with screening to be compared across a wide range of diseases and settings to better support health care decision making.

To address this knowledge gap, a microsimulation model was developed to assess the cost effectiveness of population-based, commercially available expanded RCS consisting of a 300 recessive gene panel with (1) no population screening and (2) population screening for 3 conditions only—cystic fibrosis (CF), fragile X syndrome (FXS), and spinal muscular atrophy (SMA) (hereafter referred to as 3-condition screening)—from both health service and societal perspectives. To our knowledge, this is the first comprehensive study to provide information on several important outcomes, including cost per quality-adjusted life year (QALY) gained and affected births averted with projections to year 2061 to better inform resource allocation decisions, of an expanded RCS in a single birth cohort.

Materials and Methods

Modeling approach

A microsimulation model (PreConMOD) was developed to assess the effect and cost effectiveness of population-based expanded RCS from both health service and societal perspectives. In this study, societal cost refers to

out-of-pocket costs associated with reproductive services (eg, PGT) and the cost of reduced labor force productivity because of caring for affected individuals with a genetic disease.

The PreConMOD uses statistics and simulation to predict the outcomes for individuals. Our model assumes that all prospective parents were offered expanded RCS and progress through the pathway from their first decision to undertake (or decline) expanded RCS, PGT, or prenatal diagnostic tests to potential termination of pregnancy and post-birth outcomes. The pathways in the model structure are detailed in Figures 1 and 2.

Transitions through the model were determined using a stochastic process with random samples drawn based on model parameter distributions and assigned probabilities leading to different simulation outcomes for each at-risk couple. For the base-case estimate, a 50% uptake rate of carrier screening was incorporated into the model. The probabilities used are presented in Table 1.

Study population

The base population for the PreConMOD was derived from the 2016 Australia Census data undertaken by the Australian Bureau of Statistics (ABS). The base population is a representative sample of the 2016 Australian population in which there were 212,000 families with a newborn. This study used 1% census data for 2016 and thus each record has an implied weight of 100. We identified families with children aged <1 year to estimate the number of children born in the previous year. However, this figure was somewhat an underestimate because of reasons including delay in the registration of births, undercounting because of failure to complete the census form, and deaths of children born during the year before the census. We took account of undercounting in the 2016 census data by adjusting the weights to align the total children aged <1 year with the total births registered for Australia as reported by the ABS in 2016, ie, 311,104 births.[35]

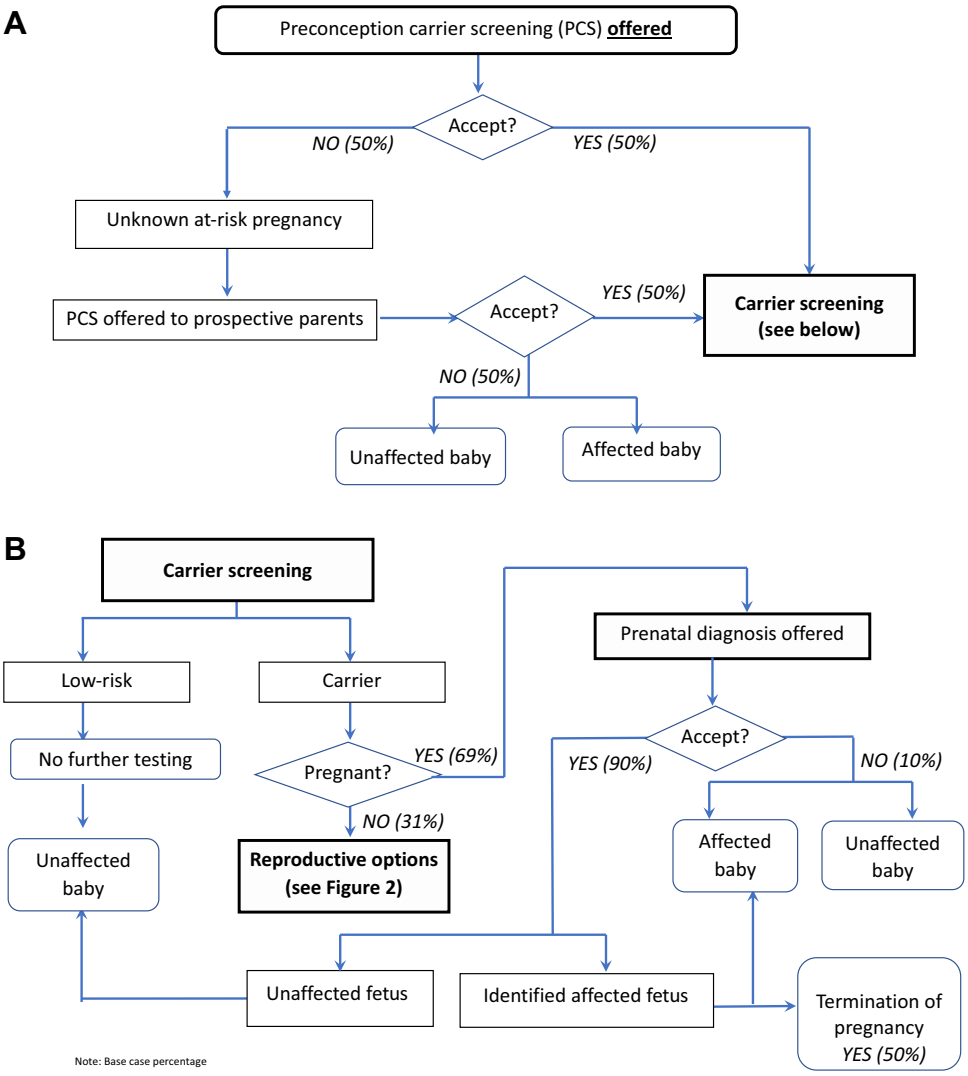

Figure 1 A. Schematic flow chart of preconception carrier screening (base case values). B. Schematic flow chart of preconception carrier screening for prospective parents.

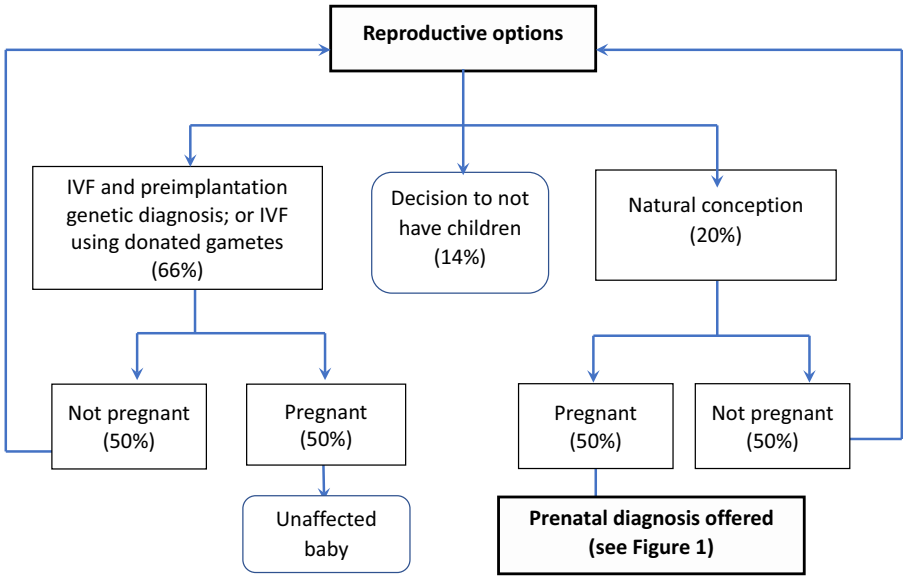

Figure 2 Schematic flow chart of reproductive options among carrier couples.

Disease list

This study used a widely available commercial expanded carrier screening panel tool covering 300 autosomal recessive and X-linked genes (Invitae Comprehensive Carrier Screen, Invitae) aimed at identifying asymptomatic individuals heterozygous for a genetic condition that could affect their offspring. The full gene list is shown in Supplemental Table 1.

Similar to a study by Beauchamp et al,[18] this study assumed perfect sensitivity and specificity for screened diseases. This approach was also supported by the Australian Government Medical Services Advisory Committee (MSAC) for the applications number 1637 (expanded reproductive carrier screening of couples for joint carrier status of genes associated with autosomal recessive and X-linked conditions)[36] and number 1585 (genetic testing for the diagnosis of early-onset or familial neuromuscular disorders).[37]

Data sources

Modeling of cost effectiveness of disease is evidence based. We retrieved published quantitative evidence for each of the 300 recessive disorders in the panel, including the incidence rate, age of disease onset, age of death, QALY effects, life expectancy, and direct and indirect costs (costs of productivity loss for caring for affected individuals with a genetic disease) (Supplementary Table 2). This entailed a literature review for all the 300 recessive disorders. When no data for a parameter for a condition was found, data for a similar condition or the average for the relevant condition group were applied.

We used databases such as OMIM, GeneReview, Orphanet, and National Organization for Rare Diseases, and expert opinion to assist in developing keywords that best define the phenotype associated with gene-related disorders for the literature review.

We focused on systematic reviews and then individual studies. Electronic databases such as OVID MEDLINE were searched for all relevant publications. The following Boolean search is an example of an OVID search: (GENE NAME) or (generic key words) and (quality of life or quality-adjusted life years or utility or EuroQol-5 Dimension or 36-Item Short Form Survey or treatment cost or health care cost or cost effective or cost-utility or cost benefit or economic evaluation or economic analysis or health economic).

We limited the search to studies conducted in English language. There was no restriction to the time frame, although more recent publications were preferred when available (ie, after 2010). Hand searching of references was also carried out to ensure that significant publications on key evidence were not missed.

Reproductive choices for at-risk couples

We modeled access to assisted reproductive treatment (ART) strategies as an option for at-risk couples who wanted to avoid having affected children. These strategies were configured to represent the likely clinical pathway of couples seeking ART in real-world settings.

However, at-risk couples may also continue with natural conception or choose not to have children. For those who achieved pregnancy after natural conception or had already conceived when they received screening results, we modeled access to prenatal diagnostic testing and the probability of termination of pregnancy if the fetus is affected.

For at-risk couples undertaking PGT, the model started with a female with a pathogenic variant undertaking 1 cycle of IVF and PGT, which could either result in pregnancy leading to a live birth or no pregnancy. In cases in which no pregnancy was achieved after 2 cycles of IVF and PGT, we

Table 1 Model parameters

Model Parameter	Description	Value, Base Case	Prior Distribution	Source
Base population, *N*	Births in 2016	212,200	N/A, fixed	ABS Census 2016[22]
Life expectancy, y	Life expectancy of general Australian population		N/A, fixed	ABS life tables 2019[23]
Health-related quality of life, mean	Health-related quality of life for general population		N/A, fixed	McCaffrey et al[24]
	<15 years old	0.96		Assumed
	15-24 years old	0.96		
	25-34 years old	0.95		
	35-44 years old	0.92		
	45-54 years old	0.89		
	55-64 years old	0.89		
	65-74 years old	0.87		
	75+ years old	0.83		
Expanded RCS screening	Proportion of couples who take-up RCS	0.5	Beta	Ioannou et al,[25] Van Steijvoort et al[26]
	Proportion of couples who become pregnant before RCS	0.69	Uniform	Archibald et al[27]
Interventions	At-risk couples who undertake ART, prenatal testing, or termination of pregnancy			Azimi et al,[28] Snowdon et al,[29] Van Steijvoort et al,[26] Taber et al[30]
	Proportion of at-risk couples using PGT (95% CI)	0.59 (0.53-0.65)	Beta	
	Proportion of at-risk couples using donor gametes (95% CI)	0.07 (0.05-0.12)	Beta	
	Proportion of at-risk couples continuing with natural conception (95% CI)	0.20 (0.16-0.26)	Beta	
	Proportion of at-risk couples who gave up having children (95% CI)	0.14 (0.04-0.18)	Beta	
	Proportion of at-risk couples who undertake prenatal diagnostic testing	0.9 ± 0.25	Beta	Archibald et al[27]
	Proportion of at-risk couples who electively terminate pregnancy	0.5 ± 0.25	Beta	Zhang et al[19]
Success rate after ART or natural conception	Proportion of at-risk couples achieving live birth after PGT-ART	0.5		Fitzgerald et al,[31] Lee et al[32]
	Proportion of at-risk couples achieving live birth after donor-ART	0.5		Hogan et al,[33] Fitzgerald et al[31]
	Proportion of at-risk couples achieving live birth with natural conception	0.5		Assumed
Discounting rate		5%		AIHW[34]
Risk of inheriting variant and associated genetic disease		0.25		

The base population of the model is a representative sample of the 2016 Australian census data, in which there were 212,000 families with a newborn. This figure was somewhat an underestimate because of reasons including delay in registration of births, undercounting because of failure to complete the Census form, and deaths of children born during the year before the census. We took account of undercounting in the 2016 by adjusting the weights to align the total children aged <1 year with the total birth registered in Australia as reported by the ABS in 2016, ie, 311,104 births.[35] At-risk couple refers to the couple in which 1 female is screened positive for X-linked conditions or both partners are identified as heterozygous for pathogenic variants from the expanded panel.

ABS, Australian Bureau of Statistics; *AIHW*, Australian Institute of Health and Welfare; *ART*, assisted reproductive treatment; *N/A*, not applicable; *PGT*, preimplantation genetic testing; *RCS*, reproductive carrier screening.

modeled undertaking IVF using donated gametes, not having children, or continuing with natural conception.

Similarly, for an at-risk couple using ART donated gametes, the model started with a female with a pathogenic variant undertaking 1 cycle of IVF using donated gametes in which it could either result in pregnancy leading to a live birth or no pregnancy. In cases in which no pregnancy was achieved, we modeled undertaking IVF and PGT, not having children, or continuing with natural conception.

At-risk couples who were unsuccessful in achieving a live birth naturally could also either undertake IVF and PGT, IVF using donated gametes, or not have children. The reproductive pathway options after carrier screening results are detailed in Figure 2.

Transition probabilities and mortality

Estimates of transition probabilities between the different reproductive choices were retrieved from published literature (Table 1). Age-specific mortality data were derived from the ABS life tables for the year 2019. Rates were converted to probabilities.

Cost inputs

In the base-case analysis, direct costs of interventions include costs of carrier screening, reproductive interventions (ie, IVF in combination with PGT or donated gametes), prenatal diagnostic testing, termination of pregnancy, and lifetime disease treatment cost. The cost of carrier screening was based on the list price in Australian dollars (AUD), ie, (AUD389) for the 3-condition screening and AUD595 per couple for expanded RCS in 2019.[38]

All costs were obtained from published literature and the Australian Medicare Benefits Schedule when applicable (Table 2). For most resources such as disease treatment costs obtained from the literature, costs were adjusted to 2019 AUD using the AIHW health inflation index.[41] In this study, costs reflect the resources required to deliver the respective interventions as well as the resources required for the treatment associated with genetic disease.

Outcome measures

We measured effectiveness of expanded RCS in terms of QALYs based on the product of health utility and time. Health utility reflects patient's quality of life, with utility values ranging from 0 (death) to 1 (perfect health), with 1 QALY defined as a year spent in perfect health. Health utility estimates were obtained from the literature.

Other secondary outcome measures included life years, number of affected births averted, and associated reduction in lifetime treatment cost as a result of carrier and prenatal screening and reproductive decisions.

Model validity

In line with the best practice recommendations for model validation,[42] experts in clinical genetics, modeling, and health economics critically reviewed the model structure, logic and and the model outcomes to ensure face validity.

Missing information imputation

For some diseases in the 300-gene panel, information on incidence rate, age of disease onset, life expectancy, health utility, and direct and indirect costs needed for model inputs were not available. Whenever this was the case, information was obtained from other related diseases with similar attributes for which data were available as has been the case in other studies.[19]

Comparators

We performed the analysis in 2 stages. In the first stage, we modeled the costs of up-front carrier screening, subsequent downstream interventions after expanded RCS, including fertility treatments, prenatal diagnostic test, and termination of pregnancy, and their outcomes (eg, cases averted because of carrier screening and downstream interventions).

In stage 2, we modeled the effect of carrier screening and reproductive decisions for the 300 genetic diseases on treatment cost and outcomes individually on a hypothetical single

Table 2 Cost of screening and interventions

Model Parameter Description	Value, AUD (Range)	Distribution	Source
Cost of expanded RCS (per couple)	595 (±50%)	Gamma	Commercial list
Cost of prenatal diagnostic testing	1600		MSAC number 1585[37]
Cost per complete cycle of PGT and ART	13,654 (±25%)	Gamma	Chambers et al,[39] Lee et al[40]
Cost per complete cycle of donor ART	13,636 (±25%)	Gamma	Chambers et al[39]
Cost of elective termination of pregnancy	625		MSAC number 1637[36]
Annual average health care spending per person	7777		AIHW[41]

AIHW, Australian Institute of Health and Welfare; *ART*, assisted reproductive treatment; *AUD*, Australian dollar; *MSAC*, Medical Services Advisory Committee; *PGT*, preimplantation genetic testing; *RCS*, reproductive carrier screening.

birth cohort. Specifically, we assessed the outcomes (ie, QALY and life-years) of the birth cohort of parents who undertake expanded RCS with comparators—(1) a counterfactual birth cohort of parents who had never had prenatal screening (ie, no population screening) and (2) another birth cohort of parents who had been screened for only 3 conditions—CF, SMA, and FXS (ie, 3-condition screening).

We included the 3-condition screening as a comparator in the analysis, because in Australia, from November 2023, public funding through Medicare will be provided for these 3 conditions. No screening was included because Australia currently has no public funded screening program as is the case in many other countries. The model was run individually for each of the 300 inheritable recessive disorders over a lifetime horizon in a single birth cohort under 3 different scenarios.

Cost effectiveness analysis

A cost effectiveness analysis was conducted using overall life-time costs and outcomes (ie, QALY, life years). Incremental cost-effectiveness ratios (ICERs) were calculated by dividing the difference in costs by the difference in QALYs between the expanded RCS and the 2 comparators, ie, (1) no screen population and (2) 3-condition screening. Total costs included cost of one-off carrier screening, subsequent downstream interventions, and lifetime disease treatment costs for each of the 300 recessive disorders in the panel. This process was repeated with 1000 iterations from which the mean estimates of the total costs and outcomes were computed.

All analyses were undertaken from both health service and societal perspectives in the Australian setting, and expanded RCS was considered cost effective if the additional cost per QALY gained was less than the threshold of a willingness-to-pay of AUD50,000, a widely used threshold for public funding.[43]

Discounting

Future costs and benefits were discounted at an annual rate of 5% as per Australian guidelines.[34]

Sensitivity analysis

Sensitivity analyses were conducted to reflect uncertainty in model inputs and to assess robustness of the model estimates. One-way sensitivity analysis include (1) varying the carrier screening uptake rate to 25%, 34%, 68%, and 75% and (2) varying the price of RCS by ± 50%.[26] We also tested a theoretical upper limit of 100% uptake rate to demonstrate the financial impact of RCS, although this is unlikely to represent what the uptake rate would be in real practice.

To assess the effect of uncertainty across all the variables in the model, we also conducted a probability sensitivity analysis using second order Monte Carlo simulation with 1000 repetitive samples. We assumed beta distributions for all probabilities and utilities whose values were bounded between 0 and 1 and gamma distributions for costs to capture its non-negative and skewed features. We estimated 95% CIs for ICERs based on their distributions using the percentile method.

All economic and sensitivity analyses were performed using SAS version 9.4 and Microsoft Excel 360 (Microsoft Corporation). All costs are presented in 2019 AUD (AUD1 = US dollar 0.7706, May 30, 2022).

Results

Base-case results

Table 3 presents the undiscounted lifetime health service costs, life-years, QALYs, and ICER results. At a 50% uptake rate, our model predicts that the expanded RCS would increase QALY by 7411 in the birth cohort at an additional cost of AUD46.5 million for screening, downstream interventions, and lifetime disease treatment. This results in an ICER of AUD6287 per QALY gained with expanded RCS compared with the 3-condition screening. Based on a willingness-to-pay of AUD50,000 per QALY, expanded RCS is likely to be cost effective compared with 3-condition screening. In addition, 1617 more affected births would be averted resulting in a net health service saving of AUD446.2 million for the cases prevented.

Compared with no population screening, our model predicted that expanded RCS is cost saving with total health service savings of AUD200.8 million and an additional 6478 QALYs gained over the cohort lifetime.

Overall, our model showed that in the absence of population carrier screening for the 300 inheritable recessive disorders, in a birth cohort of 311,104 infants in 2016, about 5292 Australian children would be born with these recessive disorders (Table 4). The total estimated lifetime health service costs attributable to 300 recessive disorders in the cohort would be AUD1460.1 million, and the indirect cost to society was AUD703.6 million.

Our findings were robust to inclusion of indirect costs. In our model, the indirect cost burden of 300 recessive disorders under the 3-condition screening was AUD627.6 million compared with AUD447.9 million with expanded RCS in 2019. Taking into account both direct and indirect costs (including out-of-pocket expenses for reproductive services) in the birth cohort, expanded RCS is a cost saving strategy with net savings of AUD336.8 million compared with 3-condition screening from the societal perspective.

The discounted net lifetime direct costs for the birth cohort showed similar findings but a smaller overall gain in QALY and costdifference, because discounting adjusted costs and outcomes that occur in the future and the cost-savings generated through future affected births averted are also valued less.

Table 3 Cost effectiveness of population-wide expanded preconception carrier screening

Panel	Up-front Carrier Screening, A$M	Downstream Intervention Costs, A$M	Total Investment, A$M	Life-Years in Thousand	Total Cases Averted, *n*	Total Disease Treatment Costs, A$M	Total QALY in Thousand	ICER (AUD) Expanded RCS	
								Versus No Population Screening	Versus 3-Condition Screening
No population screen	–	–		93.6 (77.5-112.7)	–	1460.1 (1181.1-1736.4)	62.0 (51.0-71.9)		
Three-condition combined screening	69.8	5.2	75.1	91.2 (74.5-109.1)	137 (92-190)	1132.5 (959.4-1354.0)	60.6 (50.1-72.7)		
Expanded RCS	106.8	83.8	190.7	78.2 (63.8-940.4)	1755 (1473-2113)	978.9 (874.3-1229.3)	68.0 (54.8-83.9)	Dominant (higher QALY, lower cost)	AUD6287 per QALY gained

The cost effectiveness of population-based expanded RCS was compared with "no population screening" and "3-condition screening" (combined screening panel for cystic fibrosis, spinal muscular atrophy, and fragile X syndrome) from the Australian health service perspective. The term "upfront carrier screening" refers to one-off cost of genetic screening for 300 inheritable recessive disorders and "downstream intervention" includes undertaking IVF with preimplantation genetic testing or donated gametes, prenatal diagnosis testing, and termination of affected fetus. ICER refers to the difference in the costs between expanded RCS and 3-condition combined screening or no population screening. Expanded RCS is dominant when it is associated with lower costs and improved QALY compared with no population screen. The 95% CIs in the parenthesis were calculated using 1000 bootstrapping samples.

AUD, Australian dollar; *A$M*, Australian dollars in million; *ICER*, incremental cost-effectiveness ratio; *QALY*, quality-adjusted life-year; *RCS*, reproductive carrier screening.

Table 4 Base-case estimate and projected cumulative number of children with recessive disorders and total lifetime health care costs, 2016 and 2021-2061

Panel	2016		2021-2030		2021-2040		2021-2050		2021-2061	
	Children With Inheritable Recessive Disorders, *n*	Total Disease Treatment Cost, A$M	Children With Inheritable Recessive Disorders, *n*	Total Disease Treatment Cost, A$M	Children With Inheritable Recessive Disorders, *n*	Total Disease Treatment Cost, A$M	Children With Inheritable Recessive Disorders, *n*	Total Disease Treatment Cost, A$M	Children With Inheritable Recessive Disorders, *n*	Total Disease Treatment Cost, A$M
No population screening	5292	1460.1	64,231	17,722.7	133,746	36,903.3	211,837	58,450.7	307,328	84,798.6
Three-condition screening	5154	1132.5	62,558	13,746.4	130,262	28,623.5	206,320	45,336.4	299,324	65,772.8
Expanded RCS	3537	978.9	42,930	11,882.2	89,391	24,741.9	141,584	39,188.4	205,407	56,853.4

Three-condition screening refers to combined screening panel for cystic fibrosis, spinal muscular atrophy, and fragile X syndrome.

A$M, Australian dollars in million; *RCS*, reproductive carrier screening.

Table 4 also shows the overall projected births with recessive disorders for the period 2016-2061. Based on the ABS projected births for 2021-2061, our model predicts that in the absence of population carrier screening for 300 inheritable recessive disorders, about 6154 babies will be born with these genetic diseases in 2021, increasing cumulatively to 133,745 by 2040 and to 307,328 affected births by 2061. The total estimated health service cost attributable to the 300 inheritable diseases in our model was AUD1.6 billion in 2021, increasing to AUD2.0 billion in 2040 and reaching a cumulative health service spending of AUD84.7 billion for 300 inheritable recessive disorders by 2061 (in 2019 AUD values). This means that, for each year that expanded RCS is not provided to prospective parents, on average, an additional 7500 babies with genetic disease would be born each year resulting in mean annual health care cost of AUD2068 million to the health service system. This was a conservative estimate assuming no increase in health service costs because of treatment advances or changes to the incidence rate over time.

Compared with the 3-condition screening, our model predicted that expanded RCS would avert on average, an additional 2290 affected births and reduce health service cost associated with the affected births by AUD632.0 million per year.

Sensitivity analyses

The results from the one-way sensitivity analysis (Table 5) showed that expanded RCS was cost saving if uptake increased to 69% (Scenario 3) and cost effective if uptake was at the low level of 34% (Scenario 1). At 25% uptake, the projected total health care savings because of affected births averted between 2021 and 2061 was AUD8495.9 million and increased to AUD36,984.1 million when uptake was 100%. Expanded RCS remained cost effective even if the price of expanded RCS was increased to AUD892 per couple and was cost saving if the price was less than AUD595 (Table 6). Similar outcomes were found when rates of elective termination of affected pregnancy were varied at 10% and 90% (Table 7). The cost-effectiveness planes are shown in Supplemental Figures.

We further conducted a sensitivity analysis with the price of expanded RCS set at AUD1050 (Supplemental Table 3) Results showed that an increase in price of expanded RCS to AUD1050 was likely to be cost saving compared with no population screening and cost effective with an additional cost of AUD17,318 per QALY gained when compared with 3-condition screening.

Discussion

This is the first study to comprehensively assess the cost effectiveness of population-wide expanded RCS from the health service and societal perspectives. Our base-case

Table 5 Sensitivity analysis–varying uptake rate for expanded RCS

Expanded RCS Uptake Rate	2016		2021-2030		2021-2040		2021-2050		2021-2061	
	Compared With No Screen, A$M	Compared With 3-Condition Screen, A$M	Compared With No Screen, A$M	Compared With 3-Condition Screen, A$M	Compared With No Screen, A$M	Compared With 3-Condition Screen, A$M	Compared With No Screen, A$M	Compared With 3-Condition Screen, A$M	Compared With No Screen, A$M	Compared With 3-Condition Screen, A$M
Scenario 1: 25% uptake	160.0	146.2	1942.7	1775.6	4045.3	3697.3	6407.3	5856.1	9295.6	8495.9
Scenario 2: 34 % uptake	343.8	316.9	4173.1	3846.9	8689.5	8010.2	13,763.2	12,687.3	19,967.3	18,406.4
Scenario 3: 50 % uptake	484.2	446.2	5877.5	5415.9	12,238.5	11,277.3	19,384.4	17,862.0	28,122.3	25,913.7
Scenario 4: 69% uptake	558.8	514.2	6782.3	6241.1	14,122.6	12,995.6	22,368.6	20,583.6	32,451.7	29,862.1
Scenario 5: 75% uptake	587.7	542.1	7133.8	6579.9	14,854.5	13,701.1	23,527.8	21,701.0	34,133.5	31,483.3
Scenario 6: 100% uptake	691.7	636.8	8395.5	7729.6	17,481.6	16,095.0	27,689.0	25,492.7	40,170.4	36,984.1

Costs are provided in AUD 2019 values. The additional health care savings based on cases prevented with RCS compared with no population screening and 3-condition screening (spinal muscular atrophy, cystic fibrosis, and fragile X syndrome) strategies for 2016, 2021-2061.

A$M, Australian dollars in million; *RCS*, reproductive carrier screening.

Table 6 Sensitivity analysis—varying price of expanded RCS

Panel	Up-front Carrier Screening, A$M	Downstream Intervention Costs, A$M	Total Investment, A$M	Total Disease Treatment Costs, A$M	Total QALY '000	ICER With Expanded PCS (AUD)
No population screen	–	–	–	1460.1 (1181.1-1736.4)	62.0 (51.0-71.9)	
Expanded RCS (+50%)	160.3	83.8	244.1	978.9 (874.3-1229.3)	68.0 (54.8-83.9)	Dominant (higher QALY, lower cost)
Expanded RCS (−50%)	53.4	83.8	137.2	978.9 (874.3-1229.3)	68.0 (54.8-83.9)	Dominant (higher QALY, lower cost)
Three-condition screening	69.8	5.2	75.1	1132.5 (959.4-1354.0)	60.6 (50.1-72.7)	
Expanded RCS (+50%)	160.3	83.8	244.1	978.9 (874.3-1229.3)	68.0 (54.8-83.9)	AUD13,500 per QALY gained
Expanded RCS (−50%)	53.4	83.8	137.2	978.9 (874.3-1229.3)	68.0 (54.8-83.9)	Dominant (higher QALY, lower cost)

Three-condition screen refers to combined screening panel for cystic fibrosis, spinal muscular atrophy, and fragile X syndrome. The price of expanded RCS per couple was varied between −50% and +50% of the base price at AUD595 per couple.

AUD, Australian dollar; *A$M*, Australian dollars in million; *ICER*, incremental cost-effectiveness ratio; *QALY*, quality-adjusted life-year; *RCS*, reproductive carrier screening.

Table 7 Sensitivity analysis—varying elective termination of affected pregnancy

Panel	Up-front Carrier Screening, A$M	Downstream Intervention Costs, A$M	Total Investment, A$M	Total Disease Treatment Costs, A$M	Total QALY '000	ICER With Expanded RCS (AUD)
No population screen	–	–	–	1460.1 (1181.1-1736.4)	62.0 (51.0-71.9)	
Expanded RCS (10%)	106.8	82.4	189.3	1271.1 (1061.6-1510.9)	76.7 (63.1-92.4)	AUD5371 per QALY
Expanded RCS (90%)	106.8	84.3	191.2	760.8 (638.8-908.6)	59.3 (48.5-71.7)	Lower QALY, lower cost
Three-condition screening	69.8	5.2	75.1	1132.5 (959.4-1354.0)	60.6 (50.1-72.7)	
Expanded RCS (10%)	106.8	82.4	189.3	1271.1 (1061.6-1510.9)	76.7 (63.1-92.4)	AUD20,401 per QALY
Expanded RCS (90%)	106.8	84.3	191.2	760.8 (638.8- 908.6)	59.3 (48.5-71.7)	Lower QALY, lower cost

Three-condition screen refers to combined screening panel for cystic fibrosis, spinal muscular atrophy, and Fragile X syndrome. The results show the outcomes when rates of elective termination of affected pregnancy are varied between 10% and 90%.

AUD, Australian dollar; *A$M*, Australian dollars in million; *ICER*, incremental cost-effectiveness ratio; *QALY*, quality-adjusted life-year; *RCS*, reproductive carrier screening.

estimates showed that expanded RCS is likely to be cost saving compared with no population screening and cost effective when compared with 3-condition screening. At an uptake rate of 50%, our model predicted that expanded RCS would avert one-third of affected births in the birth cohort and reduce medical spending by AUD632.0 million per year.

Our findings are consistent with previous cost-effectiveness studies that showed expanded RCS provides value for money and would prevent significantly more affected births compared with no or minimal screening (eg, CF and SMA).[18-20] For example, Zhang et al[19] modeled the comparative cost effectiveness of combined RCS for 3 recessive conditions (CF, SMA, and FXS) vs targeted testing using burden of disease measured through loss of healthy life years averted (ie, DALYs) and reduction in recurrence. Beauchamp et al[18] showed that a 176-condition expanded carrier screening panel was cost saving compared with minimal screening for CF and SMA based on savings from averting disease cases and life-years gained. However, to our knowledge, this is the first study to assess cost effectiveness of expanded RCS in QALYs gained as the health outcome. This is important because unlike other outcomes such as DALYs, which measure burden of disease, QALYs capture the lifetime benefit of an intervention (ie, carrier screening) and provide a common metric for comparisons across a wide range of disease and settings to better support health care decision making and resource allocation decisions.

Furthermore, our model incorporated relevant downstream costs and outcomes and recent publicly funded treatment cost, eg, nusinersen for SMA and gene therapy for RPE65-mediated vision loss, compared with other studies that did not model uptake rate for RCS and used a single cost estimate for all downstream interventions (eg, PGT, IVF), which may underestimate the cost effectiveness.[18,19] Our projections from 2021 to 2061 helped better inform the long-term savings with expanded RCS.

Our study was also conducted from the societal perspective to reflect the broader economic impact of recessive disorders on society. This is important because most genetic disorders are associated with significant morbidities, which often required informal care over a lifetime. This is shown in our model with indirect costs accounting for 33% of the total costs associated with recessive disorders.

We found that at an investment of AUD190.7 million per year for expanded RCS equals to 0.1% of the total health budget (in 2019-2020), reducing national spending on medical care by AUD632.0 million each year. This equates to a AUD3.40 saving for AUD1 invested.

Consistent with the study by Zhang et al,[19] this study modeled the rate of elective termination conservatively at 50%. This is somewhat lower than the MSAC application number 1637, which reported a rate of 67%, although this was only for a small sample of 4 out of 6 affected pregnancies.[37] This MSAC application to the Australian Government is for public funding of expanded reproductive carrier screening of couples for joint carrier status of genes associated with autosomal recessive and X-linked conditions (MSAC application number 1637); however, to date, it has not been funded.

Although QALYs are recognized as an important metric for assessing health gain, there are concerns that QALYs based on avoidance, termination of affected fetus places little or no value on the parent's preference of having a child with genetic disease.[44] Other studies have argued that the only quantifiable outcome with termination of an affected pregnancy is cost saving.[45] Notwithstanding the methodoilogical limitations, the use of QALYs as a standard metric of health gain enables comparisons across a wide range of disease. Although there are questions on the suitability of current QALY calculation, there is no viable alternative metric for measuring health gain with carrier screening needed to inform resource allocation decisions.[21]

Previous studies have shown that out-of-pocket cost for carrier screening can affect uptake and would disproportionately affect those on lower socio-economic status, particularly for Aboriginal Australians, the underserved, and those in rural areas.[46,47] This gap in screening uptake has been shown for other screening programs, such as prenatal aneuploidy screening and cancer screening.[48,49] Affordability of fertility treatment also affects carrier testing outcomes. Although the Australian Government provides full subsidy for PGT for at-risk couples, out-of-pocket cost of ART treatment ranging between AUD3000 and AUD4000 per fresh stimulated cycle reduces access to ART.[50]

Our study has several strengths. To our knowledge, this is the first study to comprehensively assess the cost effectiveness of expanded RCS from both health care and societal perspectives. This model included societal costs, reported QALYs as outcomes, and used the most contemporary evidence to inform our model parameters.

This study has several limitations. Similar to all decision-analytical models, our cost-effectiveness analysis relies on key assumptions because of the varying quality of evidence and considerable uncertainty associated with rare conditions. Second, we included only productivity costs. Thus, societal costs and cost effectiveness from the societal perspective are conservative. However, we have sought to address, to some degree, the uncertainty in these parameters using sensitivity analysis, which yielded similar results to our base-case analysis. Third, we have assumed both members of the couple were tested simultaneously although studies have shown that some partners may choose not to be tested or terminate an affected pregnancy even after being informed by a positive test result.[27] Finally, the model assumed perfect sensitivity and specificity for screened diseases as has been done in other studies.[18,51]

In conclusion, our model showed that at a 50% uptake rate, expanded RCS for recessive disorders is cost effective compared with 3-condition screening or no population screening from the health care and societal perspectives.

Expanded RCS is projected to avert significantly more affected births and reduce health care costs beyond those expected from the 3-condition screening.

Data Availability

The authors confirm that all data for parameters are fully available without restriction, and the Census is available by application under the provisions of the Australian Bureau of Statistics.

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Author Information

D.S. conceived the study, provided leadership in executing the study and critically reviewed the manuscript. E.L. led and reviewed the literature, collected data, led the modeling analysis, wrote codes, generated and interpreted the results, and led the writing of the manuscript. J.P. reviewed the literature and provided critical review of the manuscript. S.K. and R.S. provided technical advice, wrote codes, and provided critical review of the manuscript. J.M., N.L., and M.H. provided critical review of the manuscript.

Ethics Declaration

Not applicable. Ethical approval was not required for this study, since it is an economic model that uses published evidence and data from public sources including the Census which is available by application under the provisions of the Australian Bureau of Statistics (ABS).

Conflict of Interest

The authors declare no conflicts of interest.

Additional Information

The online version of this article (https://doi.org/10.1016/j.gim.2023.100813) contains supplementary material, which is available to authorized users.

Affiliations

[1]Centre for Economic Impacts of Genomic Medicine, Macquarie University, Sydney, New South Wales, Australia; [2]National Centre for Social and Economic Modelling (NATSEM), University of Canberra, Canberra, Australian Capital Territory, Australia; [3]Kinghorn Centre for Clinical Genomics, Garvan Institute of Medical Research, Darlinghurst, New South Wales, Australia; [4]Centre for Medical Research, The University of Western Australia, Perth, Western Australia, Australia; [5]Genetic Alliance Australia, Sydney, New South Wales, Australia

References

1. Costa T, Scriver CR, Childs B. The effect of Mendelian disease on human health: a measurement. *Am J Med Genet*. 1985;21(2):231-242. http://doi.org/10.1002/ajmg.1320210205
2. Kumar P, Radhakrishnan J, Chowdhary MA, Giampietro PF. Prevalence and patterns of presentation of genetic disorders in a pediatric emergency department. *Mayo Clin Proc*. 2001;76(8):777-783. http://doi.org/10.1016/S0025-6196(11)63220-5
3. Liu Z, Zhu L, Roberts R, Tong W. Toward clinical implementation of next-generation sequencing-based genetic testing in rare diseases: where are we? *Trends Genet*. 2019;35(11):852-867. http://doi.org/10.1016/j.tig.2019.08.006
4. Wojcik MH, Schwartz TS, Yamin I, et al. Genetic disorders and mortality in infancy and early childhood: delayed diagnoses and missed opportunities. *Genet Med*. 2018;20(11):1396-1404. http://doi.org/10.1038/gim.2018.17
5. Grody WW, Thompson BH, Gregg AR, et al. ACMG position statement on prenatal/preconception expanded carrier screening. *Genet Med*. 2013;15(6):482-483. http://doi.org/10.1038/gim.2013.47
6. Kaback MM. Population-based genetic screening for reproductive counseling: the Tay-Sachs disease model. *Eur J Pediatr*. 2000;159(suppl 3):S192-S195. http://doi.org/10.1007/pl00014401
7. Antonarakis SE. Carrier screening for recessive disorders. *Nat Rev Genet*. 2019;20(9):549-561. http://doi.org/10.1038/s41576-019-0134-2
8. Cao A, Rosatelli MC, Monni G, Galanello R. Screening for thalassemia: a model of success. *Obstet Gynecol Clin North Am*. 2002;29(2):305-328, vi-vii. http://doi.org/10.1016/s0889-8545(01)00006-7
9. Nazareth SB, Lazarin GA, Goldberg JD. Changing trends in carrier screening for genetic disease in the United States. *Prenat Diagn*. 2015;35(10):931-935. http://doi.org/10.1002/pd.4647
10. Lazarin GA, Haque IS, Nazareth S, et al. An empirical estimate of carrier frequencies for 400+ causal Mendelian variants: results from an ethnically diverse clinical sample of 23,453 individuals. *Genet Med*. 2013;15(3):178-186. http://doi.org/10.1038/gim.2012.114

11. Haque IS, Lazarin GA, Kang HP, Evans EA, Goldberg JD, Wapner RJ. Modeled fetal risk of genetic diseases identified by expanded carrier screening. *JAMA*. 2016;316(7):734-742. http://doi.org/10.1001/jama.2016.11139
12. Kraft SA, Duenas D, Wilfond BS, Goddard KAB. The evolving landscape of expanded carrier screening: challenges and opportunities. *Genet Med*. 2019;21(4):790-797. http://doi.org/10.1038/s41436-018-0273-4
13. Gregg AR, Aarabi M, Klugman S, et al. Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2021;23(10):1793-1806. Published correction appears in *Genet Med*. 2021;23(10):2015. http://doi.org/10.1038/s41436-021-01203-z
14. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Genetic carrier screening. RANZCOG. Accessed January 30, 2022. https://ranzcog.edu.au/wp-content/uploads/2022/05/Genetic-carrier-screeningC-Obs-63New-March-2019_1.pdf
15. Rowe CA, Wright CF. Expanded universal carrier screening and its implementation within a publicly funded healthcare service. *J Community Genet*. 2020;11(1):21-38. http://doi.org/10.1007/s12687-019-00443-6
16. Wienke S, Brown K, Farmer M, Strange C. Expanded carrier screening panels-does bigger mean better? *J Community Genet*. 2014;5(2):191-198. http://doi.org/10.1007/s12687-013-0169-6
17. Dive L, Newson AJ. Ethical issues in reproductive genetic carrier screening. *Med J Aust*. 2021;214(4):165-167.e1. http://doi.org/10.5694/mja2.50789
18. Beauchamp KA, Johansen Taber KA, Muzzey D. Clinical impact and cost-effectiveness of a 176-condition expanded carrier screen. *Genet Med*. 2019;21(9):1948-1957. Published correction appears in *Genet Med*. 2022;24(4):968. http://doi.org/10.1038/s41436-019-0455-8
19. Zhang L, Bao Y, Riaz M, et al. Population genomic screening of all young adults in a health-care system: a cost-effectiveness analysis. *Genet Med*. 2019;21(9):1958-1968. Published correction appears in *Genet Med*. 2019;21(9):2162-2163. http://doi.org/10.1038/s41436-019-0457-6
20. Wang T, Bahrampour M, Byrnes J, Scuffham P, Kirk E, Downes M. Economic evaluation of reproductive carrier screening for recessive genetic conditions: a systematic review. *Expert Rev Pharmacoecon Outcomes Res*. 2022;22(2):197-206. http://doi.org/10.1080/14737167.2022.1993063
21. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes*. Oxford University Press; 2015.
22. Commonwealth of Australia, Australian Bureau of Statistics. 2071.0 - Census of Population and Housing: Reflecting Australia - Stories from the Census, 2016. Accessed December 11, 2019. https://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/2071.0~2016~Main%20Features~Snapshot%20of%20Australia,%202016~2
23. Commonwealth of Australia, Australian Bureau of Statistics. 3302.0.55.001 - Life Tables, States, Territories and Australia, 2015-2017. Accessed January 30, 2022. https://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/2071.0~2016~Main%20Features~Snapshot%20of%20Australia,%202016~2
24. McCaffrey N, Kaambwa B, Currow DC, Ratcliffe J. Health-related quality of life measured using the EQ-5D-5L: South Australian population norms. *Health Qual Life Outcomes*. 2016;14(1):133. http://doi.org/10.1186/s12955-016-0537-0
25. Ioannou L, McClaren BJ, Massie J, et al. Population-based carrier screening for cystic fibrosis: a systematic review of 23 years of research. *Genet Med*. 2014;16(3):207-216. http://doi.org/10.1038/gim.2013.125
26. Van Steijvoort E, Chokoshvili D, Cannon WJ, et al. Interest in expanded carrier screening among individuals and couples in the general population: systematic review of the literature. *Hum Reprod Update*. 2020;26(3):335-355. http://doi.org/10.1093/humupd/dmaa001
27. Archibald AD, Smith MJ, Burgess T, et al. Reproductive genetic carrier screening for cystic fibrosis, fragile X syndrome, and spinal muscular atrophy in Australia: outcomes of 12,000 tests. *Genet Med*. 2018;20(5):513-523. Published correction appears in *Genet Med*. 2018;20(11):1485. http://doi.org/10.1038/gim.2017.134
28. Azimi M, Schmaus K, Greger V, Neitzel D, Rochelle R, Dinh T. Carrier screening by next-generation sequencing: health benefits and cost effectiveness. *Mol Genet Genomic Med*. 2016;4(3):292-302. http://doi.org/10.1002/mgg3.204
29. Snowdon C, Green JM. Preimplantation diagnosis and other reproductive options: attitudes of male and female carriers of recessive disorders. *Hum Reprod*. 1997;12(2):341-350. http://doi.org/10.1093/humrep/12.2.341
30. Taber KAJ, Beauchamp KA, Lazarin GA, Muzzey D, Arjunan A, Goldberg JD. Clinical utility of expanded carrier screening: results-guided actionability and outcomes. *Genet Med*. 2019;21(5):1041-1048. http://doi.org/10.1038/s41436-018-0321-0
31. Fitzgerald O, Harris K, Paul RC, Chambers GM. Assisted reproductive technology in Australia and New Zealand 2015. National Perinatal Epidemiology and Statistics Unit, the University of New South Wales Sydney; 2017. Accessed November 10, 2022. https://npesu.unsw.edu.au/sites/default/files/npesu/data_collection/Assisted%20Reproductive%20Technology%20in%20Australia%20and%20New%20Zealand%202015.pdf
32. Lee E, Illingworth P, Wilton L, Chambers GM. The clinical effectiveness of preimplantation genetic diagnosis for aneuploidy in all 24 chromosomes (PGD-A): systematic review. *Hum Reprod*. 2015;30(2):473-483. http://doi.org/10.1093/humrep/deu303
33. Hogan RG, Wang AY, Li Z, et al. Oocyte donor age has a significant impact on oocyte recipients' cumulative live-birth rate: a population-based cohort study. *Fertil Steril*. 2019;112(4):724-730. http://doi.org/10.1016/j.fertnstert.2019.05.012
34. Australian Government Department of Health and Aged Care. The Pharmaceutical Benefits Advisory Committee (PBAC) guidelines. Pharmaceutical benefits Advisory Cimmittee. Published September 2016. Accessed May 22, 2022. https://pbac.pbs.gov.au
35. Commonwealth of Australia, Australian Bureau of Statistics. 3301.0 - Births, Australia, 2016 Australian Bureau of Statistics. Published December 13, 2017. Accessed December 11, 2019. https://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/3301.0Main+Features12016?OpenDocument=
36. Medical Services Advisory Committee. 1637 - Expanded reproductive carrier screening of couples for joint carrier status of genes associated with autosomal recessive and X-linked conditions. Australian Government. Department of Health and Aged Care. Updated October 31, 2022. Accessed November 10, 2022. http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1637-public
37. Medical Services Advisory Committee. 1585 - Genetic testing for the diagnosis of early-onset or familial neuromuscular disorders. Australian Government. Department of Health and Aged Care. Updated October 17, 2022. Accessed November 10, 2022. http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1585-public
38. National Center for Biotechnology Information. Invitae comprehensive carrier screening. Genetic Testing Registry. Accessed November 10, 2022. https://www.ncbi.nlm.nih.gov/gtr/tests/569389/overview
39. Chambers GM, Ho MT, Sullivan EA. Assisted reproductive technology treatment costs of a live birth: an age-stratified cost–outcome study of treatment in Australia. *Med J Aust*. 2006;184(4):155-158. http://doi.org/10.5694/j.1326-5377.2006.tb00174.x
40. Lee E, Costello MF, Botha WC, Illingworth P, Chambers GM. A cost-effectiveness analysis of preimplantation genetic testing for aneuploidy (PGT-A) for up to three complete assisted reproductive technology cycles in women of advanced maternal age. *Aust N Z J Obstet Gynaecol*. 2019;59(4):573-579. http://doi.org/10.1111/ajo.12988
41. Australian Institute of Health and Welfare. Health expenditure Australia 2018-2019. Health and welfare expenditure series no.66. Cat. no. HWE 80. Australian Institute of Health and Welfare. 2020. Accessed November 10, 2022. https://www.aihw.gov.au/getmedia/a5

cfb53c-a22f-407b-8c6f-3820544cb900/aihw-hwe-80.pdf.aspx?inline=true#:~:text=During%202018%E2%80%9319%2C%20more%20than,24.5%25%20in%202017%E2%80%9318

42. Eddy DM, Hollingworth W, Caro JJ, et al. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force–7. *Med Decis Making*. 2012;32(5):733-743. http://doi.org/10.1177/0272989X12454579
43. Grosse SD. Assessing cost-effectiveness in healthcare: history of the $50,000 per QALY threshold. *Expert Rev Pharmacoecon Outcomes Res*. 2008;8(2):165-178. http://doi.org/10.1586/14737167.8.2.165
44. Petrou S. Health economic aspects of late preterm and early term birth. *Semin Fetal Neonatal Med*. 2019;24(1):18-26. http://doi.org/10.1016/j.siny.2018.09.004
45. Grosse SD, Wordsworth S, Payne K. Economic methods for valuing the outcomes of genetic testing: beyond cost-effectiveness analysis. *Genet Med*. 2008;10(9):648-654. http://doi.org/10.1097/gim.0b013e3181837217
46. Roder D. Comparative cancer incidence, mortality and survival in Indigenous and non-indigenous residents of South Australia and the Northern Territory. *Cancer Forum*. 2005;29(1):7-9.
47. Taylor RJ, Mamoon HA, Morrell SL, Wain GV. Cervical screening by socio-economic status in Australia. *Aust N Z J Public Health*. 2001;25(3):256-260. http://doi.org/10.1111/j.1467-842x.2001.tb00573.x
48. Maxwell S, Brameld K, Bower C, et al. Socio-demographic disparities in the uptake of prenatal screening and diagnosis in Western Australia. *Aust N Z J Obstet Gynaecol*. 2011;51(1):9-16. http://doi.org/10.1111/j.1479-828X.2010.01250.x
49. Callander E, Bates N, Lindsay D, et al. Long-term out of pocket expenditure of people with cancer: comparing health service cost and use for indigenous and non-indigenous people with cancer in Australia. *Int J Equity Health*. 2019;18(1):32. http://doi.org/10.1186/s12939-019-0931-4
50. Chambers GM, Hoang VP, Zhu R, Illingworth PJ. A reduction in public funding for fertility treatment-an econometric analysis of access to treatment and savings to government. *BMC Health Serv Res*. 2012;12:142. http://doi.org/10.1186/1472-6963-12-142
51. Hogan GJ, Vysotskaia VS, Beauchamp KA, et al. Validation of an expanded carrier screen that optimizes sensitivity via full-exon sequencing and panel-wide copy number variant identification. *Clin Chem*. 2018;64(7):1063-1073. http://doi.org/10.1373/clinchem.2018.286823