# How do different approaches to the economic modelling of genetic and genomic tests drive differences in results?

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**Amber Salisbury**

*A thesis submitted to fulfil the requirements for the degree of Doctor of Philosophy*

School of Public Health, Faculty of Medicine and Health

The University of Sydney

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# Statement of originality

This is to certify that to the best of my knowledge, the content of this thesis is my own work.

This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

Amber Salisbury

Date 21/02/2025

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# Authorship attribution statement

In accordance with University of Sydney Higher Degree Research policy, this thesis contains a combination of published manuscripts and standalone chapters. I, Amber Salisbury, led each of the included studies and chapters, which were conducted under the supervision of Associate Professor Sarah Norris, Professor Kirsten Howard, Associate Professor Alison Pearce, Dr Anagha Killedar and in collaboration with other co-authors. The specific contributions of each author for each chapter are described below.

**Chapter 1** was written by Amber Salisbury (AS), with feedback from Sarah Norris (SN), Kirsten Howard (KH), Alison Pearce (AP) and Anagha Killedar (AK).

**Chapter 2** contains a manuscript entitled *Comprehensive review of economic models of genetic and genomic testing.* AS, SN and KH conceived the aim and methods. AS conducted the review and analysis and wrote the manuscript. Amy Von Huben (AVH) contributed to the double data extraction. Feedback was provided by SN, KH, AP, AVH and AK.

**Chapter 3** includes the publication titled *Impact of structural differences on the modeled cost-effectiveness of noninvasive prenatal testing.* AS, SN and KH conceived the aim and methods. AS built the models, conducted the analysis and wrote the manuscript. AS, KH, AP and SN interpreted the analysis and commented on and revised the manuscript.

**Chapter 4** includes the publication titled *Public perspectives around prenatal screening of chromosomal abnormalities: A focus group study comparing metropolitan and rural/regional areas in Australia*. AS, SN, AP and KH conceived the aim and methods. AS led the focus group discussions, with help from Alexis Johnson and Hovea Winston (HW). AS and HW double coded the transcripts. AS conducted the analysis and wrote the manuscript. All authors provided comments on and revised the manuscript.

**Chapter 5** includes the publication titled *Australian preferences for prenatal screening: A discrete choice experiment comparing metropolitan and rural/regional areas.* AS, SN, AP and KH conceived

the aim and methods. AS built the survey, conducted the analysis and wrote the manuscript. AS, SN, AP and KH interpreted the analysis and provided comments on and revised the manuscript.

**Chapter 6** is titled *Integrating intermediate outcomes into economic models: A case study using prenatal screening.* AS, SN, AP and KH conceived the aim and methods. AS conducted the review, built the models, conducted the analysis and wrote the manuscript. AS, SN, AP, AK and KH interpreted the analysis and provided comments on and revised the manuscript.

**Chapter 7** This chapter was written by AS, with feedback from SN, KH, AP and AK.

I attest that the statements above are correct.

Name: Amber Salisbury

Date: 21/02/2025

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Name: Sarah Norris

Date: 21/02/2025

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# First-author publications arising from thesis

The following first-author publications arose from this thesis:

- **Salisbury A**, Pearce A, Howard K, Norris S. Impact of structural differences on the modeled cost-effectiveness of noninvasive prenatal testing. *Medical Decision Making*. 2024; 44: 811-27.
- **Salisbury A**, Winston H, Johnson A, Pearce A, Howard K, Norris S. Public perspectives around prenatal screening of chromosomal abnormalities: A focus group study comparing metropolitan and rural/regional areas in Australia. *Australian and New Zealand Journal of Obstetrics and Gynaecology.* 2025; doi:10.1111/ajo.13935.
- **Salisbury A**, Norris S, Pearce A, Howard K. Australian preferences for prenatal screening: A discrete choice experiment comparing metropolitan and rural/regional areas. *Applied Health Economics and Health Policy*. 2025; 1-14.

# List of abbreviations

| | |
|---|---|
| AUD | Australian Dollar |
| CBA | Cost-Benefit Analysis |
| CEA | Cost-Effectiveness Analysis |
| cFTS | Combined First Trimester Screening |
| CMA | Cost-Minimisation Analysis |
| CUA | Cost-Utility Analysis |
| DCE | Discrete Choice Experiment |
| DNA | Deoxyribonucleic Acid |
| GBP | Great Britain Pound |
| HTA | Health Technology Assessment |
| ICER | Incremental Cost-Effectiveness Ratio |
| MBS | Medical Benefits Schedule |
| MCDA | Multicriteria Decision Analysis |
| MSAC | Medical Services Advisory Committee |
| NGS | Next Generation Sequencing |
| NICE | National Institute for Health and Care Excellence |
| NIPT | Non-Invasive Prenatal Testing |
| NMB | Net Marginal Benefit |
| NMBA | Net Marginal Benefit Analysis |
| PBAC | Pharmaceutical Benefit Advisory Committee |
| PROM | Patient-Reported Outcome Measure |
| PRL | Procedure Related Loss |
| QALY | Quality-Adjusted Life Year |
| QASE | Quality-Adjusted Survival Equivalents |
| RNA | Ribonucleic Acid |
| T13 | Trisomy 13 |
| T18 | Trisomy 18 |
| T21 | Trisomy 21 |
| UK | United Kingdom |
| USD | United States Dollar |
| WES | Whole Exome Sequencing |

| | |
|---|---|
| WGS | Whole Genome Sequencing |
| WTA | Willingness To Accept |
| WTP | Willingness To Pay |

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# Abstract


## *Background*

In many countries, including Australia, health technologies undergo evaluation by a Health Technology Assessment (HTA) body to inform decisions around public funding. These evaluations include an assessment of the cost-effectiveness (value for money) of a health intervention. Traditionally, economic evaluations were designed to assess a test or treatment for a single condition and an 'average person', where the costs and outcomes followed straightforward trajectories. Genetic and genomic tests, however, can assess multiple genes and produce results for multiple conditions, including variants of unknown significance and secondary findings, with dynamic impacts on costs and outcomes. Current economic evaluation methods struggle to deal with this complexity.

Several reviews have examined the challenges associated with economic evaluations of genetic and genomic testing, consistently identifying three main areas of concern: 1) the complexity of study questions and implications for model structures that accurately account for the aforementioned complexity; 2) the need for models to capture a broad range of relevant upstream and downstream outcomes and costs; 3) lack of data. These challenges are particularly critical in economic modelling, the primary method used for economic evaluations in public funding applications in Australia. While the challenges have been thoroughly described, the solutions remain underdeveloped.

## *Objectives*

The overarching objective of the current research was to examine the impact of different approaches to economic modelling of genetic and genomic tests and the potential for these to lead to different public funding decisions for these tests. The focus was on two key challenges of economic methods: (1) Model Structure and (2) Selection of Outcomes. Specifically, the research was designed to explore the following phenomena:

1. Model Structure: how model structures with differing levels of complexity affect model findings; and

2. Selection of Outcomes: how the use of a broader range of outcomes (especially intermediate outcomes) from genetic and genomic testing can be incorporated within economic models.

## *Methods*

This thesis begins with a comprehensive review of economic models for genetic and genomic testing. The review examined approaches used in published economic models and evaluates progress in overcoming key challenges in this field. Via this review, non-invasive prenatal testing (NIPT) was identified as a case study for further exploration of model structure and selection of outcomes. The subsequent stages were: (a) developing multiple model structures of NIPT for the detection of Down syndrome, and populating these models with consistent parameters to allow the impact of selected structural variations to be assessed; (b) conducting three focus group discussions with the Australian public to inform the development of a discrete choice experiment (DCE); (c) the DCE, which valued intermediate outcomes through willingness to pay estimates (WTP); and (d) extending two models developed in stage (a) by incorporating the WTP estimates derived from the DCE within both net marginal benefit and cost-utility analyses. Scenario analyses were conducted to determine the effect of these estimates on model findings and potential funding decisions.

## *Results*

### *Comprehensive review*

The review of published economic models for genetic and genomic testing revealed substantial variation in modelling approaches, often with inadequate justification for structural choices. Many models did not incorporate process and intermediate outcomes due to insufficient data about the value of these outcomes, and uncertainty in the methods used to incorporate these values. NIPT emerged as an area with many published economic analyses using multiple modelling techniques. The cost-effectiveness results for NIPT showed wide variance, ranging from cost saving to AUD1,917,495 per Down syndrome diagnosis. Based on these findings, NIPT was chosen as the case study to explore the complexities of model structure and selection of outcomes.

### *Model structure*

Model structuring choices substantially affected results and likely policy decisions. The incremental cost-effectiveness ratio (ICER) ranged from NIPT being dominated (more expensive and less effective) using a microsimulation with five health states, to being cost-effective at the commonly referenced threshold of AUD50,000 per quality adjusted life year (QALY) gained using decision trees with three and five health states, to AUD80,431 per QALY gained (more expensive and more effective) using a microsimulation with three health states.

*Focus groups*

The focus groups revealed that the Australian public values a broad range of prenatal screening impacts, with notable differences between metropolitan and rural communities regarding access considerations. Based on these discussions, eight attributes were selected for inclusion in the DCE: scope of testing, false positive rate, false negative rate, inconclusive rate, information on fetal sex, number of screening tests per pregnancy, wait time, and cost of the screening test.

*Discrete choice experiment*

The false positive rate, false negative rate, and cost influenced both metropolitan and rural preferences significantly. In addition, the scope of conditions covered, inconclusive rate, and wait times influenced rural preferences significantly. The number of screening tests and information on the sex of the fetus were not significant factors for either group. The WTP estimates for intermediate outcomes were AUD13 for rural and AUD16 for metropolitan participants to avoid a 1% increase in false positive rate, and AUD51 for rural participants to avoid a 1% increase in inconclusive rate.

*Extending the model to include DCE results of intermediate outcomes*

The impact of including intermediate outcomes varied based on the model structure. In the base case analysis (a microsimulation with five health states), the inclusion of intermediate outcomes caused the cost-utility analysis ICER and net marginal benefit to become less favourable. However, this change was unlikely to affect funding decisions. In the scenario analysis (a decision tree with three health states), incorporating intermediate outcomes increased the ICER from AUD48,927 to

AUD130,043/QALY gained, and caused the net marginal benefit to shift from positive (0.37) to negative (-1.49), decreasing the likelihood of public funding for NIPT.

*Conclusion*

Firstly, using NIPT as a case study, this research demonstrates that while simpler models are easier to implement, they can fail to capture important elements of genetic and genomic tests that affect costs and outcomes. In contrast, more complex models can provide a more accurate representation of the influential elements of these tests but required greater resources and expertise. This thesis therefore provides evidence to model builders and policymakers that, due to their impact on model findings, investing in more complex models of genetic and genomic testing is crucial for informed policy decisions.

Secondly, integrating intermediate outcomes into cost-utility analysis and net marginal benefit analysis substantially impacted cost-effectiveness results. These findings provide direct evidence in support of the formal consideration of intermediate outcomes within public funding decisions about genetic and genomic testing.

In summary, the research described in this thesis produced valuable insights that should be used to improve economic models of genetic and genomic testing, supporting more robust policy decisions.

# Thesis roadmap

This thesis consists of seven chapters, each addressing the issue of uncertainty in economic evaluation models from a different perspective. This roadmap presents a brief outline of how each chapter contributes to the overall thesis (**Figure 1**).

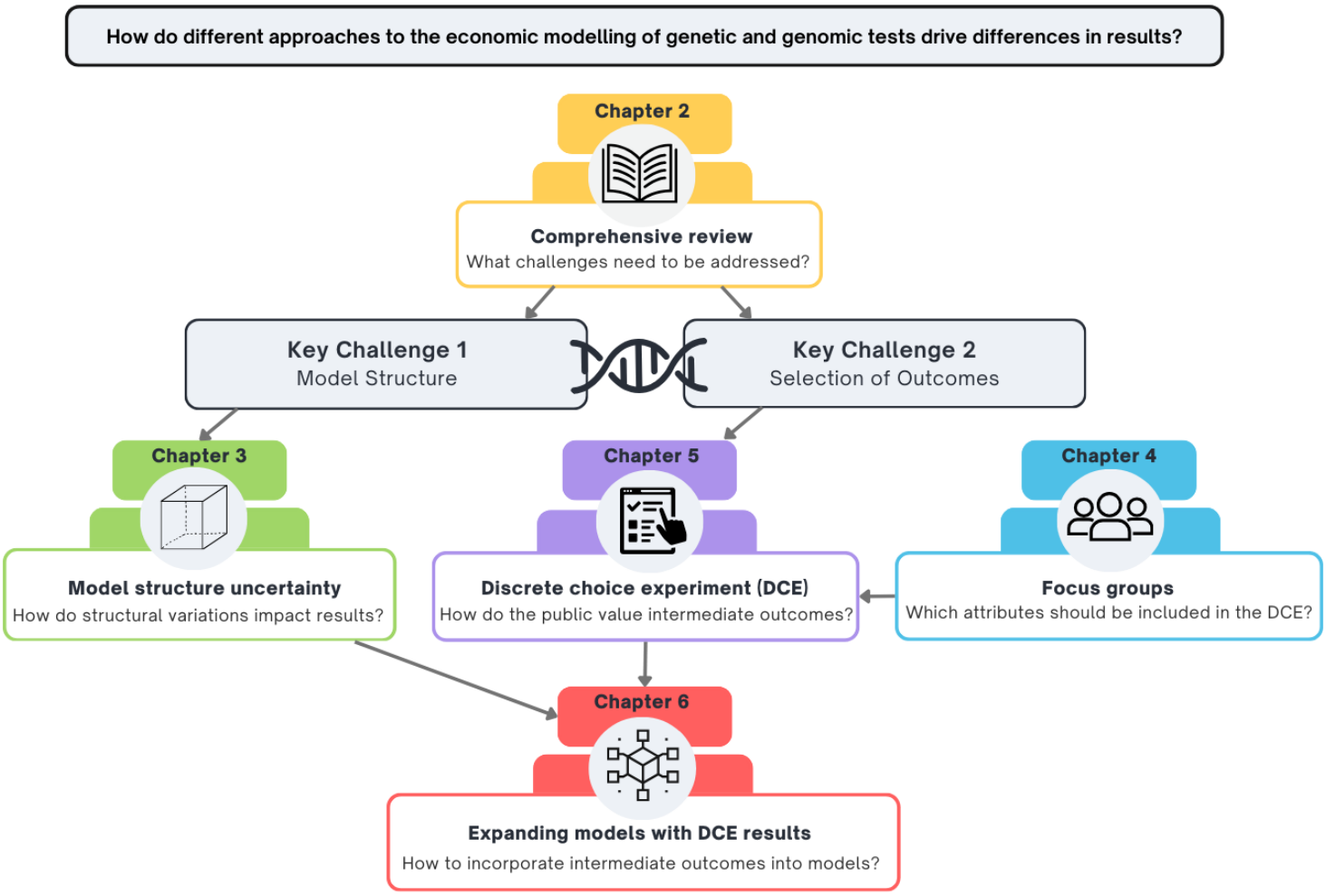


**Figure 1. Diagram illustrating how the chapters of this thesis combine to meet the overall aim.**

**Chapter 1:** Introduction to health economics and the challenges within genetic and genomic testing

This chapter introduces key concepts relevant to this thesis: the role of health economic models in public funding decisions, the nature of uncertainties in health economic modelling, and the specific challenges associated with economic modelling in genetic and genomic testing.

**Chapter 2:** Comprehensive review of economic models of genetic and genomic testing

This chapter, formatted as an unpublished manuscript, presents a comprehensive review of published economic models in genetic and genomic testing across multiple clinical conditions and testing purposes. It then identifies a case study that facilitates the exploration of challenges associated with economic modelling in genetic and genomic testing in the subsequent chapters. It describes how non-invasive prenatal testing (NIPT) was selected as the case study due to the large number of published economic models, structural variations among these models, and the potential of NIPT to have impacts that extend beyond the clinical diagnosis.

**Chapter 3:** Impact of structural differences on the modelled cost-effectiveness of non-invasive prenatal testing

This chapter includes the following published article:

> **Salisbury A**, Pearce A, Howard K, Norris S. Impact of structural differences on the modeled cost-effectiveness of noninvasive prenatal testing. *Medical Decision Making*. 2024; 44: 811-27.

This article presents a systematic review of economic models comparing NIPT with conventional screening. It identifies key structural variations, including the number of health states and modelling techniques. Based on these insights, new demonstration models for NIPT with varied structures were developed. These models were populated with consistent parameters to allow for comparison of the impact of selected structural variations on results.

**Chapter 4:** Public perspectives around prenatal screening of chromosomal abnormalities: A focus group study comparing metropolitan and rural/regional areas in Australia.

This chapter includes the following published article:

> **Salisbury A,** Winston H, Johnson A, Pearce A, Howard K, Norris S. Public perspectives around prenatal screening of chromosomal abnormalities: A focus group study comparing metropolitan and rural/regional areas in Australia. *Australian and New Zealand Journal of Obstetrics and Gynaecology*. 2025; doi: 10.1111/ajo.13935.

This article explores Australian perspectives on prenatal screening through focus groups, highlighting differences between metropolitan and rural/regional communities. The review in Chapter 2 revealed that economic evaluations often overlook process and intermediate outcomes, primarily due to limited data on the value associated with these outcomes. This focus group study served as an initial step toward understanding these values, with geographical location playing a key role within this context. These findings informed the development of the DCE presented in the subsequent chapter.

**Chapter 5:** Australian preferences for prenatal screening: A discrete choice experiment comparing metropolitan and rural/regional areas

This chapter includes the following published article:

> **Salisbury A**, Norris S, Pearce A, Howard K. Australian preferences for prenatal screening: A discrete choice experiment comparing metropolitan and rural/regional areas. *Applied Health Economics and Health Policy*. 2025; 1-14.

This article presents a DCE that explored preferences for prenatal screening, with participants recruited from metropolitan and rural/regional areas across Australia. The DCE quantifies the value of prenatal screening features through the model coefficients, WTP estimates, and benefit to harm trade-offs. The WTP estimates for intermediate outcomes were intended to be incorporated into the demonstration models described in Chapter 3.

**Chapter 6**: Integrating intermediate outcomes into economic models: A case study using prenatal screening

This chapter incorporates WTP estimates from Chapter 5 into selected economic models (described in Chapter 3). Two alternative analytical approaches are presented to explore the impact of including these estimates within the economic models: cost-utility analysis and net marginal benefit analysis. Both approaches allow for the consideration of the impacts of intermediate outcomes in economic evaluations, providing a more comprehensive assessment of prenatal screening. From a practical standpoint, cost-utility analysis was determined to be the more feasible option.

**Chapter 7:** Discussion and conclusions

The final chapter synthesises the key contributions of this research to the literature around economic evaluation methods, explores the implications for NIPT research and policy in particular, and for health economics and public funding decisions on genetic and genomic tests more broadly. This chapter outlines the strengths and limitations of the current research and concludes with recommendations for future research.

Figures and tables are numbered consecutively throughout the thesis, except in published articles inserted as PDFs. Each chapter's references are numbered separately.

# Chapter 1:

# Introduction

This chapter introduces key concepts relevant to this thesis: the public funding of health technologies in Australia and internationally, the different types of uncertainty in economic models, and challenges specific to genetic and genomic testing, examining how the literature has progressed in addressing these challenges.

## Public funding of health technologies

In many countries, including Australia, England, Canada, and the United States, health technologies undergo evaluation by a Health Technology Assessment (HTA) body to inform decisions around public funding.[1] The International Network of Agencies for Health Technology Assessment and Health Technology Assessment International recently developed an internationally accepted definition of HTA:[2]

> HTA is a multi-disciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle. The purpose is to inform decision-making in order to promote and equitable, efficient, and high-quality health system.

Health technologies, as defined within this framework, refer to interventions developed to prevent, diagnose, or treat medical conditions; promote health; provide rehabilitation; or organise healthcare delivery. These interventions can include tests, devices, medicines, vaccines, procedures, programs, or healthcare systems.

In Australia, the primary HTA bodies are the Medical Services Advisory Committee (MSAC) and the Pharmaceutical Benefits Advisory Committee (PBAC). MSAC evaluates new medical procedures, technologies, and services to inform decisions on public funding under the Medicare Benefits Schedule (MBS),[3] while PBAC evaluates pharmaceuticals for public funding under the Pharmaceutical Benefits Scheme and vaccines for funding under the National Immunisation Program.[4] Both HTA bodies rely on structured assessments comprising of five main sections:[3, 4]

1. *Context:* this section outlines the intended use of the health technology and provides a rationale for its public funding;
2. *Clinical Evaluation:* this section assesses the comparative health gain, examining the magnitude and clinical significance of the technology's effectiveness and safety;
3. *Economic Evaluation:* this section focuses on assessing the cost-effectiveness of the health technology;
4. *Budget Impact:* this section predicts the expected usage of the health technology and assesses its overall financial impact on the healthcare budget; and
5. *Other relevant considerations:* other factors may be considered when making funding decisions. These factors are classified as "less-readily quantifiable" and can include the overall confidence in the evidence and assumptions which have been made, equity, the value of knowing, (for tests) the presence of effective alternatives, relevant barriers or facilitators to the uptake of the technology, and broader impacts of the health technology. Broader impacts can include intermediate outcomes, such as the psychological impacts of receiving a false positive result, or process outcomes, such as reduced wait times. These impacts are recommended to be submitted within the supplementary materials of the application (i.e. as a standalone analysis).

## Economic evaluations and theoretical foundations

This research focused on the *Economic Evaluation* section of the HTA process in Australia. This section assesses whether the additional benefits of the proposed health technology justify the additional costs (i.e., value for money).[5] The fundamental objective of all economic evaluations is to identify, measure, value and compare the costs and consequences of the alternatives under consideration.

Economic evaluations are generally guided by one of the two key theoretical approaches: welfarist or extra-welfarist.[5] Welfarism is grounded in welfare economics, which aims to maximise social welfare based on individual utility.[6] In this context, economic evaluations consider all consequences of health and healthcare that affect individual utility, including health outcomes,

process outcomes (e.g., wait times), intermediate outcomes (e.g., anxiety from a false positive), and outcomes outside of the healthcare sector (e.g., environmental impacts). In contrast, the extra-welfarist approach aims to maximise health based on societal values.[7, 8] This approach limits the scope of economic evaluations to outcomes that directly contribute to health gain, focusing on improvements in quality and length of life.[9]

Several types of economic evaluations are used in healthcare decision-making.[5] These include:

- cost-utility analysis (CUA), in which outcomes are valued in multidimensional measures that incorporate survival and quality of life/morbidity (e.g., QALYs, quality-adjusted life years), consistent with the extra-welfarist approach;
- cost-effectiveness analysis (CEA), in which outcomes are measured in natural units of health outcomes, such as strokes avoided or life-years gained, generally consistent with the extra-welfarist approach;
- cost-benefit analysis (CBA), in which outcomes are valued in monetary terms to allow a broader range of societal benefits and costs to be included, consistent with the welfarist approach.
- net marginal benefit analysis (NMBA), in which outcomes are valued in monetary terms by using a pre-defined threshold (e.g., the monetary value of a QALY), maintaining the extra-welfarist approach.
- cost-minimisation analysis (CMA), which assumes (or has evidence for) outcomes being equal across interventions and focuses on comparing costs.

HTA bodies in Australia recommend an extra-welfarist approach as it aligns with their primary goal of maximising health outcomes within the constraints of available healthcare resources.[3, 4] This approach is shaped by societal values, representing the viewpoint of the general public as taxpayers who fund the healthcare system. When feasible, they recommend a CUA, because it allows for the comparison of interventions across healthcare contexts using a common unit of measurement, thereby

facilitating decisions on resource allocation. However, government decision-making tends to favour the use of CBA, adopting a welfarist perspective.[10]

Decision analytic models are commonly used to conduct the economic evaluations within HTA submissions. These models establish a set of mathematical relationships between various entities (typically health states or pathways), characterising the range of effects of different health interventions on outcomes.[5] They are particularly useful in scenarios where direct evidence to inform the economic evaluation is unavailable and evidence is drawn from multiple sources. For instance, there may be no single trial comparing the technology and the comparator; stronger evidence may be available from a systematic review than from a single trial; the health technology may not have been introduced; it may be impractical to measure factors such as long-term intervention effects; and studies involving certain populations may be deemed unethical.[11, 12] Decision analytic models provide a structured, often simplified, representation of the relevant healthcare pathway, an example is shown in **Figure 2**.

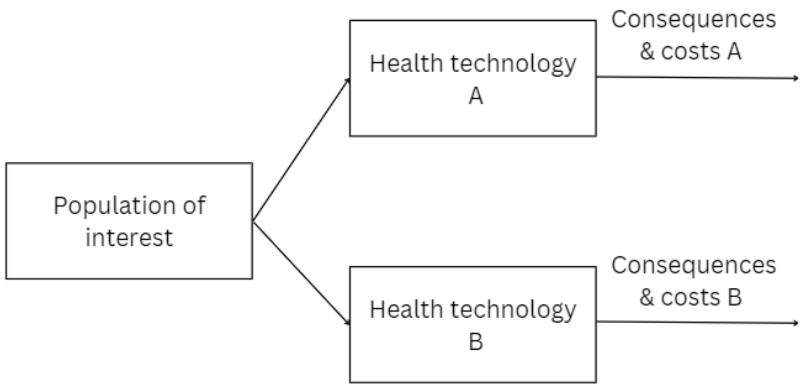


**Figure 2. Structured representation of a health pathway comparing health technologies**

The modeller can select a modelling technique (the underlying framework of the model and modelling processes) to represent the intervention pathway. This choice depends on the purpose of the economic evaluation and the nature of the condition and intervention, with certain modelling

techniques being more appropriate for certain scenarios (**Table 1**).[13, 14] Model complexity increases as the choice moves from cohort-based decision trees, to models incorporating ongoing risk over time, to individual-level modelling techniques, and finally to system-based models. While increased model complexity offers greater flexibility and the ability to capture additional elements, such as more health states over longer periods of time, it also requires more evidence to populate the model. This leads to greater time and expertise needed for development and can be more computationally demanding. In principle, it is argued that the least complicated technique that appropriately represents influential components of the decision problem should be chosen.[3-5]

**Table 1. Descriptions of the different modeling techniques used for economic evaluations.**

| Modeling technique | Definition and suitable context | Limitations | Example |
|---|---|---|---|
| **Cohort-based models** | | | |
| Decision Tree | Cohort-based model that characterises possible outcomes in terms of alternative branches. It is often used for short and fixed time horizons. | Becomes increasingly complex and difficult to manage with complex or long-term scenarios.<br>Limited ability to capture ongoing or recurring risks.<br>Does not inherently capture patient heterogeneity. | Used within a NICE application to evaluate the cost-effectiveness of different antibiotics for treating acute urinary tract infections, where patient outcomes are measured within a short timeframe.[15] |
| Markov model | Cohort-based model that captures ongoing risk over time and is based on a series of health "states" that a patient can occupy over a series of discrete time periods (cycles). These models are commonly used in long-term chronic diseases. | Assumes fixed intervals for transitions.<br>"Memoryless" property ignores previous states.<br>Complexity increases with more states.<br>Does not inherently capture patient heterogeneity. | Markov model assessing kidney transplants vs dialysis, running over six years, using one year cycles.[16] |
| Partitioned survival analysis | A model used to assess survival outcomes by partitioning patients into groups based on their treatment responses and analysing the time spent in different health states. This technique is often used for treatments such as cancer therapies where survival outcomes are crucial for decision-making. | Does not explicitly model transitions between health states.<br>Patient heterogeneity limited to treatment responses and survival.<br>Assumes survival curves are independent of previous events. | An application made to MSAC for the public funding of brexucabtagene autoleucel for patients with relapsed or refractory mantle cell lymphoma.[17] The end points include "progression free survival" and "overall survival". |
| **Individual-based models** | | | |

| | | | |
|---|---|---|---|
| Microsimulation | A model which tracks individual simulated patients over time, allowing for the incorporation of 'memory' and accounting for patient heterogeneity. | Computationally intensive for large populations.<br>Requires detailed individual-level data.<br>Results may vary due to random variation. | A microsimulation model was used to estimate the cost-effectiveness of population mammography screening.[18] The model considered individuals with varying risk, breast density, or comorbidities. |
| Discrete event simulation models | A type of microsimulation model that tracks individual simulated patients and predicts the time until the occurrence of the next event. These models typically allow for the examination of individual entities and their interactions within a system. | Complex to design and validate.<br>Requires detailed event timing and interactions.<br>Results are sensitive to assumptions about event sequences. | Discrete event simulation model used for the assessment of smoking cessation in Japan. The model simulation starts with each smoker attempting to quit.[19] If the attempt was successful, a time to relapse was assigned. If unsuccessful, a time interval until the next attempt to quit and the next cessation strategy were assigned. |
| Dynamic transmission models | A model which captures individual-level characteristics and behaviours within a population. This model relaxes the assumption that individuals are independent from one another, which is particularly useful for modelling infectious diseases. | Requires extensive data on transmission and interactions.<br>Results re sensitive to contact pattern assumptions.<br>Computationally demanding for large-scale models. | Susceptible–Infectious–Recovery transmission dynamic model to assess effectiveness of lockdown during the SARS-CoV-2 pandemic.[20] |

| | | | |
|---|---|---|---|
| **System-based models** | | | |
| System dynamic model | Continuous simulation method describing relationships among variables in complex systems, often with feedback loops and nonlinear relationships. | Oversimplifies individual behaviours.<br>Requires clear understanding of system relationships.<br>Difficult to validate due to model complexity. | A model that determines how emergency and on-demand care is currently configured and what policies could alleviate pressure on the health system.[21] |

Abbreviations: MSAC, Medical Services Advisory Committee; NICE, National Institute for Health and Care Excellence; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2.

## Uncertainty in health economic modelling

As decision analytic models typically rely on evidence from multiple sources and a number of assumptions, they are inherently uncertain. The stages of building a model consist of deciding on the analytical methods, creating the structure, and populating the model.[22] Different choices can be made at each stage of model development, with each choice leading to uncertainties.

### *Types of Uncertainty*

Based on the stages of model development, there are three broad forms of uncertainty.

- *Methodological uncertainty:* this relates to variations in the analytic methods or approaches used to construct the model, such as the chosen perspective (e.g. societal or healthcare funder), discount rates (e.g. 3% or 5%), and the approach for valuing health gains (e.g. life years or QALYs).
- *Parameter uncertainty:* this relates to the precision of numerical input values and is influenced by the quality and applicability of the underlying data.
- *Structural uncertainty:* this involves the assumptions and simplifications made within the model and the relationships between input parameters. Different structures often stem from different interpretations of the disease's natural history or clinical practices (e.g., the inclusion of different health states), differences in available data (e.g., incorporating individual risk factors), and the methods used to model intervention effects (e.g., how intervention effects are extrapolated over time).

Researchers may interpret structural uncertainty in different ways.[23, 24] In this research, an operational interpretation of structural uncertainty was adopted, because it encompasses aspects of uncertainty that are often overlooked.[25] This interpretation involves defining the sequential steps of the structuring process, highlighting where uncertainties may arise.

- *Conceptual modelling*: this involves selecting the clinically and economically important health states and relevant patient attributes to include within the model.

- *Structural choices:* this step determines how model inputs are interrelated and estimated, such as how time affects the likelihood of an event and the selection of appropriate survival models. For instance, modellers may select different ways to represent time-dependent risks, such as how the risk of death or relapse increases as a disease progresses.[26] The exponential model provides a straightforward approach by assuming constant risk over time. For more dynamic situations, the Weibull model can capture changing risks as time progresses. In cases where multiple patient characteristics influence outcomes differently over time, the Cox proportional hazards model offers additional flexibility, making it particularly valuable for complex disease patterns with risk factors that vary among patient populations.
- *Choice of modelling technique*: this final step involves selecting the underlying structure, such as choosing between a decision tree or a Markov model. This choice affects the complexity of the model and is influenced by decisions made in the previous two steps. In practice, the choice of modelling technique may also influence what the modeller decides to include within their model.

To illustrate the distinction between structural and parameter uncertainty, consider the selection of patient characteristics for a model. Patient characteristics include sociodemographic factors such as age and gender, clinical factors such as comorbidities, and lifestyle behaviours such as smoking or alcohol consumption. Within this thesis, the selection of characteristics to include in a model is referred to as structural uncertainty. In contrast, whether the assigned value for these characteristics accurately reflects its true value constitutes parameter uncertainty.

### *Assessment of uncertainty*

In Australia, HTA guidelines provide clear guidance on how to approach both parameter and methodological uncertainty, but guidance on structural uncertainty remains ambiguous.[3, 4, 27, 28] To reduce methodological uncertainty, MSAC and PBAC recommend conducting scenario analysis, providing direction on how to choose variables to be assessed and the way results should be presented.[3, 4] To reduce parameter uncertainty, MSAC and PBAC recommend presenting univariate deterministic sensitivity analysis for all input parameters, or natural groups of parameters. They also

advise using multivariate sensitivity analysis to test the combined effects of uncertainty around the true inputs, and probabilistic analysis if appropriate. Regarding structural uncertainty, it is suggested that scenario analyses are conducted based on alternative model structure assumptions. However, the definition of these structural assumptions is unclear, and creating multiple alternative model structures is unlikely to be feasible. Despite this lack of clarity in addressing structural uncertainty, MSAC and PBAC guidelines state that the assessment of structural uncertainties should take priority over probabilistic sensitivity analyses of numerical inputs related to parameter uncertainty. The importance of structural uncertainty in public funding decisions is highlighted through a review of MSAC public summary documents.[25] These documents frequently cite uncertainty in model predictions related to model structuring and inputs for baseline progression as a key reason for deferred or rejected outcomes. The ambiguity in both the definition of structural uncertainty and its evaluation is not limited to HTAs in Australia; it is a global issue, and the need for clearer guidance is increasingly recognised.[20, 21, 29, 30]

## Challenges of health economic modelling of genetic/genomic tests

Genetic and genomic testing refers to tests that analyse deoxyribonucleic acid (DNA), ribonucleic acid (RNA), or chromosomes.[131] The approaches for testing can be grouped into cytogenic (chromosomes) and molecular techniques (DNA or RNA from any tissue, such as blood or saliva), in both of which testing can occur at various scales. For molecular techniques, testing can occur along the following spectrum:

- specific location in one gene: targeted variant analysis;
- an entire gene – single gene testing;
- multiple genes – polygenic risk scores or multi-gene panels;

[1] DNA contains the genetic instructions needed for an organism to grow, live, and reproduce. It consists of two strands that twist together to form a double helix. In contrast, RNA is usually single-stranded and helps carry the instructions from DNA to make proteins in cells. Chromosomes, which are found in the nucleus of cells, are tightly coiled packages of DNA and proteins that carry genetic information.

- the protein coding region – whole exome sequencing (WES); or
- the genome – whole genome sequencing (WGS).

Within the literature, the terms "genetic" and "genomic" are often used interchangeably. Within this thesis, "genetic testing" refers to the analysis of a single gene or small gene panels (up to 10 genes), while "genomic testing" refers to medium gene panels (>10 genes) through to WES or WGS. Depending on the scale of testing chosen, different technologies can be used, the most recent technological advancement being next-generation sequencing (NGS). NGS is a DNA sequencing technology that uses parallel sequencing of multiple small fragments of DNA.[32] This technology has enabled exome and genome sequencing to occur at a greater speed than in traditional methods, and its cost has declined significantly since it was introduced.[33] However, it is important to note that NGS is not always the most suitable option for testing. Several cost-effectiveness studies have shown that while NGS strategies, including WES and WGS, tend to improve diagnostic yield, they also increase healthcare costs.[34] Additionally, these strategies present technical challenges, such as data interpretation, and raise ethical concerns related to variants of unknown significance, incidental findings, patient consent, and data privacy.[35] To add to the complexity, genetic and genomic testing can be performed in multiple clinical contexts: screening or diagnosis of genetic disorders, newborn screening, carrier screening, genetic risk assessment and treatment planning (including pharmacogenomics), and across different populations: embryos, fetuses, children/adolescents, adults, affected individuals and unaffected individuals.[31]

The complexity of genetic and genomic testing brings to light the challenges of current economic modelling methods. Several reviews have explored these challenges in the context of genetics and genomics, focusing on different clinical areas, populations, and scales or technologies of testing.[34, 36-39] These reviews consistently identify similar challenges, though they present varying categorisations or interpretations. Phillips et al.[36] focused on NGS (i.e., type of technology), including multi-gene panels, WES and WGS. Their review provides a straightforward and clear categorisation of the challenges in economic modelling of NGS tests, which can be extended to genetic and genomic

testing across clinical contexts, noting that complexities generally increase as the scale of testing increases. Phillips et al.'s review divided the challenges into three main groups, as outlined below.

### *1. Study questions and model structure*

Traditionally, economic models were designed to assess a single test for a single condition and treatment, for an "average" person, following a straightforward cost and outcome trajectory. Genetic and genomic tests, however, can assess multiple genes and produce results for multiple conditions, including variants of unknown significance and secondary findings. Each of these results may have distinct clinical trajectories and thus different costs and outcomes. Due to the individualised nature of genomic testing, patient heterogeneity is likely to play a considerable role in the test's cost-effectiveness. Consequently, capturing the complexities of the actual clinical pathway within economic models can be hard, and simple cohort structures, such as decision trees, may not adequately resolve these complexities.

### *2. Selection and measurement of costs and outcomes*

There may be both upstream and downstream costs that are difficult to measure, such as of data storage, variant reinterpretation, additional testing, or the costs of managing secondary findings. Genetic and genomic tests can also produce a broad range of outcomes that extend beyond clinically actionable results for patients. These outcomes may include both clinically non-actionable (e.g., no treatments are available) and non-clinical results. The literature presents various categorisations and terminologies for these outcomes, with terms such as "personal utility" and "non-health outcomes" often used in differing and interchangeable ways. In this thesis, patient outcomes that extend beyond the clinically actionable results are defined as follows:

- value of knowing (often referred to as personal utility[40]);
- intermediate impacts (e.g., the psychological impacts of receiving false positive or inconclusive results, sometimes considered "non-health outcomes"[41]);
- process impacts (e.g., wait times or the convenience of a procedure, sometimes considered "non-health outcomes"[41]); and

- outcomes outside the health sector (often referred to as "non-health outcomes", such as effects on employment and education).

There are also family spillover effects and societal outcomes that extend beyond the individual patient. However, these were not considered in the current research.

*3. Data availability and quality*

Data on key variables such as the prevalence of mutations, clinical and non-clinical utility of testing, and ancestry-specific inputs may be of poor quality, scarce or non-existent. Results for multiple conditions also creates joint uncertainties that may require complex statistical estimation.

### *How have the challenges been addressed?*

Phillips et al.[36] and several other reviewers[23, 26-28] showed how the challenges described above were addressed in the literature and/or provide recommendations on how they should be overcome.

*1. Study questions and model structure*

Phillips et al.[36] found that of the 15 studies included in their literature review, two addressed the issue of complex model structure by narrowing the research question and analysing hypothetical scenarios. Boutelle et al.[40] suggested that model structure is not an issue unique to genetic and genomic testing, but is present across several health technologies with complicated pathways, such as public health interventions. Consequently, they recommended improving the understanding of the complexities involved and applying current methods appropriately. Johnson et al.[38] found substantial variation in the complexity of models and quality of reporting. Model complexity ranged from simple decision trees to individual-level microsimulations that compared between 2 and >20 alternative interventions. The authors suggest that studies using models with higher levels of complexity and/or quality should act as exemplars for future research. They also recommend using scenario analyses as a method to assess structural uncertainty in these models.

*2. Selection and measurement of costs and outcomes*

Phillips et al.[36] found that no study explicitly addressed the issues associated with measuring costs and outcomes. Boutelle et al. [40] suggested the difficulty in estimating costs is a practical challenge for economic evaluation rather than one requiring methods development. Both Boutelle et al. [40] and Weyman et al.[34] suggested that the broad range of outcomes linked to genetic and genomic testing presents a unique challenge for health economic modelling. These reviews emphasise the need for methodological advancements to incorporate these outcomes into decision-making, and propose that direct inclusion into economic models is a viable approach.[34, 40]

*3. Data availability and quality*

Phillips et al.[36] found that only one study addressed the issues associated with data availability and statistical analysis through a value of information analysis. Johnson et al.[38] similarly recommended the use of value of information analysis to quantify the additional research required in this space. Boutell et al.[40] highlighted the need for solutions to strengthen the evidence base, suggesting novel trial designs and real-world evidence collection as potential approaches.

## Measuring and valuing outcomes in the context of genetic/genomic testing

As described above, genetic and genomic testing can result in a broad range of outcomes which can be difficult capture. Two main approaches are available for measuring outcomes: patient-reported outcome measures (PROMs) and preference elicitation techniques.[5]

PROMs are self-completed questionnaires used in clinical trials and routine care to capture patients' health perspectives. Generic measures, such as the EuroQol 5-Dimension (EQ-5D)[42] and Health Utilities Index (HUI),[43] are commonly used for utility measurement in QALY calculations. However, these measures are limited in scope, primarily capturing clinically actionable outcomes and potentially missing broader impacts of genetic testing. Disease-specific measures, such as the Cancer Therapy Evaluation Program (CTEP) Symptom Questionnaire[44] and St. George's Respiratory Questionnaire (SGRQ),[45] are designed for specific conditions but face limitations in genetic and genomic testing contexts due to their narrow focus on single-condition clinical outcomes.

Preference elicitation techniques include both revealed and stated preferences.[46] Revealed preferences are based on real-world choices and behaviours, derived from actual decision-making data. In contrast, stated preferences are gathered by asking people about their preferences in hypothetical situations, using methods such as discrete choice experiments (DCEs), best-worst scaling, surveys, ranking exercises and contingent valuation. Stated preference methods offer several key benefits, including the ability to evaluate a technology before implementation, applicability when real-world data is poor, and flexibility in outcome selection. Within genetic and genomic testing evaluation, DCEs have emerged as the predominant stated preference method and are seeing increasing adoption across healthcare settings.[41, 47]

## Missing pieces

Several reviews have examined the challenges associated with economic evaluation of genetic and genomic testing, [23, 26-2836] consistently identifying similar issues, which align with the three categories outlined by Phillips et al.[36]: study questions and model structure; outcomes and costs; and data availability. These challenges are particularly critical in economic modelling, the primary method used for economic evaluations in public funding applications in Australia. Despite numerous reviews, these challenges have persisted over time.[40]

The challenges of (1) Model Structure and (2) Selection of Outcomes can be overcome through modelling approaches, while data availability and costs largely require improvements in the evidence base. First, while genetic and genomic testing pathways are known to be complex, there is uncertainty about how much of this complexity needs to be captured in economic models, and how different structural choices might affect both model results and subsequent public funding decisions. More broadly, there is insufficient guidance on addressing structural uncertainty. Second, although DCEs have been proposed to capture broader outcomes associated with genetic and genomic testing, there is no consensus on whether or how these findings should be integrated into economic models informing public funding decisions. Furthermore, it remains unclear whether including these broader outcomes affects model results and funding recommendations.

## Research objectives

The overarching objective of this research was to examine the impact of different approaches to economic modelling of genetic and genomic tests and the potential for these to lead to different public funding decisions for these tests. The focus was on two key challenges of economic methods: (1) Model Structure and (2) Selection of Outcomes. Specifically, the research was designed to explore the following phenomena:

- Model Structure: how model structures with differing levels of complexity affect model findings; and
- Selection of Outcomes: how the use of a broader range of outcomes (especially intermediate outcomes) from genetic and genomic testing can be incorporated within economic models.

Overall, the research described in this thesis was designed to provide evidence to support the development of clearer guidance on managing structural uncertainty and considering broader outcomes within public funding decisions about genetic and genomic testing.

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# Chapter 2:

# A comprehensive review of economic models of genetic and genomic testing

The primary purpose of the work described in this chapter was to identify a case study to facilitate exploration of key challenges associated with economic modelling of genetic or genomic testing. First, a comprehensive review of economic models of genetic or genomic testing across all clinical conditions and testing purposes was conducted. The review explored how genetic and genomic testing models have been approached, in terms of model structure and the inclusion of intermediate and process outcomes. It also examined the variation in cost-effectiveness results for the same clinical condition and test, because this may indicate model inconsistencies and reflect challenges in economic modelling. The review identified non-invasive prenatal testing (NIPT, a blood test that screens for chromosomal conditions in a fetus) as a procedure with many published economic models, subjected to multiple modelling techniques, and with wide variance in cost-effectiveness results (ranging from cost saving to USD1,278,330 per Down syndrome diagnosis). Based on the findings of this review, NIPT was selected as the case study to be explored in the current research.

## Authors

**Amber Salisbury**, Amy Von Huben, Anagha Killedar, Alison Pearce, Kirsten Howard, Sarah Norris

## Abstract

**Background:** Expanded genetic/genomic testing through the adoption of next-generation sequencing (NGS) has the potential to deliver more precise clinical care than current practice. Three types of challenges have been identified in evaluating the cost-effectiveness of NGS: use of complex model structures, selection and measurement of costs and outcomes (such as process and intermediate outcomes), and data availability. These challenges have led to inconsistent approaches to economic modelling, with unknown impacts on model findings.

**Objectives:** To examine (1) how economic evaluations of genetic/genomic testing have been approached, (2) whether these evaluations capture the impacts of process and intermediate outcomes; (3) the extent to which modelling techniques have been justified and tested, and (4) the extent to which cost-effectiveness results vary across evaluations of the same clinical condition and test.

**Methods:** A comprehensive review of economic models published between 2010 and June 2022 (identified via EMBASE, Medline, SCOPUS, and EconLit).

**Results:** The 231 included studies covered a variety of clinical purposes. Decision trees and Markov models were the most common modelling techniques, with 12% of studies justifying their approach. Eighty-one per cent of studies conducted a deterministic sensitivity analysis, 59% conducted a probabilistic analysis and 38% conducted a scenario analysis. Three per cent of studies included the impacts of intermediate and/or process outcomes. Few studies were identified that evaluated the same clinical condition and test; therefore, few comparisons could be made.

**Conclusion:** Published economic models of genetic/genomic testing involve a wide range of modelling approaches and inconsistent justifications for their methods. It is recommended that model developers consider and justify their choice of modelling technique and discuss the possible impacts of those choices on the modelled results. More consistent application of deterministic, probabilistic,

and scenario analyses is important. Further research is recommended to develop solutions for incorporating intermediate and process outcomes into economic evaluations.

## Introduction

Rapid advances in deoxyribonucleic acid (DNA) sequencing technology have the potential to transform how we deliver health care. Next-generation sequencing (NGS), which uses parallel sequencing of multiple small fragments of DNA[1], has enabled reliable, high-speed sequencing, and is largely responsible for a precipitous fall in the direct cost of sequencing a whole human genome (from USD100 million in 2001 to USD700 in 2020).[2] However, as with any transformative health technology, all the domains that contribute to an assessment of the value[3] of genomic testing must be considered: effectiveness (i.e., test performance and impact on subsequent care), safety (e.g., the potential for increased rates of inconclusive or incidental findings[4]), all costs (i.e., beyond the direct cost of sequencing), patient/consumer preferences, and health system efficiency (e.g., optimal timing of testing in the clinical pathway, and whether alternative genetic or biochemical tests are sufficient).

Phillips et al. identified three main challenges to economic evaluations of NGS tests.[5] The first challenge is the wide range of ways the technology can be used, which gives rise to multiple potential pathways of care, costs, comparators and outcomes. These factors are reflected in complex model structures. The second challenge relates to measuring costs and outcomes. There may be both upstream and downstream costs that are difficult to measure, such as data storage, variant reinterpretation, additional testing, or the consequences of secondary findings. Additional outcomes that are not typically measured may be relevant to patients and consumers, such as reducing the time to diagnosis (often referred to as the "diagnostic odyssey"), intermediate outcomes such as the psychological impacts of receiving false positive results, or process outcomes such as the wait time and inconvenience of a procedure. The third challenge relates to data availability and quality, which tends to be low for NGS tests in general, and even more so for rare conditions. As Phillips et al. noted, each of these challenges introduces significant uncertainty into economic evaluations of NGS.

Phillips et al. also examined how the challenges described above were addressed in the literature and found very few health economic analyses that attempt to do this.[5] Of the 15 studies included in their literature review, two studies addressed the issue of complex model structure (by narrowing the research question and analysing hypothetical scenarios), no study explicitly addressed

the issues associated with measuring costs and outcomes, and only one study addressed the issues associated with data availability and statistical analysis (through a value of information analysis).

Several other reviews have explored economic evaluations within this context, with most focusing on the cost-effectiveness of a specific genetic or genomic test.[6-8] Reviews that explored the challenges of economic evaluations focused on specific populations,[9] clinical areas,[10, 11] and/or types of testing.[5, 12] More recently, an umbrella review[13] identified challenges aligning with those described by Phillips et al.[5] It has been recommended that further research focuses on identifying viable solutions in addition to examining the solutions used in published studies.[5]

Due to the increase in publications in this area since Philips et al., this comprehensive review aimed to provide an updated summary of health economic models in genetic and genomic testing. It identified economic models across multiple areas of genetic and genomic testing, enabling a comparison of modelling approaches across and within contexts. Further, this review aimed to expand on Phillips et al.'s review by extracting additional information to determine if progress has been made towards the authors' recommendations.

## Methods

### *Research aims*

This study aimed to evaluate the following: (1) how economic evaluations of genetic/genomic testing have been approached, (2) whether these evaluations capture the impacts of process and intermediate outcomes, (3) whether they incorporate uptake rates, (4) the extent to which modelling techniques have been justified and tested, and (5) the extent to which cost-effectiveness results vary across evaluations of the same clinical condition and test.

### *Review type*

A comprehensive review was conducted to identify relevant studies. The review followed methods similar to a systematic review, but given its very broad scope, capture of all available studies cannot be guaranteed. This approach consisted of a comprehensive and transparent search process and appraisal.[14] The authors developed and agreed upon a detailed protocol prior to the search. Additional guidance was obtained from librarians at the University of Sydney.

### *Information sources*

Comprehensive searches were conducted in four databases: EMBASE, Medline, SCOPUS and EconLit. In addition, the included studies from relevant systematic reviews were scanned for additional studies that might not have been identified in the formal literature search.

The search strategy was based on two concepts: genetic/genomic testing, and economic evaluation. During initial scoping searches it was observed that many economic evaluations of non-invasive prenatal testing (NIPT) did not use common terminology for genomic testing. Consequently, specific additional search terms were included for NIPT. The search covered material published from the 1st of January 2010 to the 15th of June 2022. The search was limited to 2010 because by this year NGS technology was becoming widely adopted in clinical practice and economic evaluations conducted before this time were unlikely to capture NGS-based tests. The search terms are presented in Supplementary materials (Section A)

### *Eligibility criteria*

Model-based economic evaluations considering costs and consequences were eligible for inclusion in this review (cost-effectiveness; cost-utility, cost-benefit; cost-consequence; and threshold analyses). Trial-based studies, costing studies and budget impact analyses were excluded. All populations and approaches to genetic/genomic testing (i.e., from single gene to whole genome sequencing) were included to enable a comparison of approaches across and within clinical areas. Economic evaluations of pathogen testing were excluded because these involved sequencing of non-human genes. Economic evaluations of proprietary gene expression profiling tests were excluded because these are "black box" technologies that hinder identification of the type of sequencing undertaken. Non-human studies and those published in languages other than English were also excluded. The full eligibility criteria can be found in the Supplementary materials (Section B).

### *Study selection and data extraction*

Studies were selected following PRISMA reporting guidelines.[15] A single reviewer (AS) screened all titles and abstracts against the inclusion/exclusion criteria. Studies were marked as "included", "maybe", and "excluded" using EndNote software. A second reviewer (SN) screened all studies marked as "included" and "maybe". Where disagreements occurred, a third reviewer (KH) was consulted. Full texts were obtained for eligible studies based on the title/abstract screen (AS). A data extraction template was created within Microsoft Excel (SN, KH, AS) and tested on a sample of publications prior to use (AS). Following revisions, a single reviewer (AS) extracted the data. A second reviewer checked all publications had been correctly classified in terms of their clinical purpose (SN) and reviewed all data fields on a random sample of 10% (SN and AVH). A third reviewer (KH) resolved any queries. The data extraction fields consisted of the following: Key components (time horizon, perspective, cost and outcome discount rate, type of economic analysis and sensitivity analysis); Population and testing (clinical condition, clinical purpose of testing, initial population to be tested, test, scale of gene analysis); Uptake method; Inclusion of the wider impacts of testing (defined as process outcomes and intermediate outcomes); Modelling technique (type of technique, justification, testing in sensitivity analysis, inclusion in discussion); Results (cost-effective

as reported by author; incremental cost-effectiveness ratio [ICER]; ICER threshold, conclusion). In addition, relevant quotes that described the justification and testing of modelling techniques were extracted. The data extraction template can be found in the Supplementary materials (Section C).

### *Quality assessment*

Quality assessment was performed using the Drummond checklist.[16] A rating scale, developed by Doran et al.[17], was used to attribute a maximum possible score of 1 point to each item on the checklist. The aggregate results provide an assessment of quality: poor (1–3 points), average (4–7 points), and good (8–10 points).[17]

### *Data classification*

To ensure consistency, pre-defined lists were created for data entry where possible. The clinical purpose categories were based on those suggested by Korf and Irons.[18] The study type, modelling technique, perspective, and sensitivity analysis were based on those presented by Drummond et al.[16] The modelling technique was recorded as per the authors' description (decision tree, Markov model, microsimulation, discrete event simulation, partition survival analysis, system dynamics model, and dynamic transmission model). Assumptions were made if the paper only used broad terms to describe the model (e.g., "decision analytical modelling"). A decision tree model was assumed to have been applied if there was a short time horizon and no further information to indicate otherwise (e.g., time cycles or half-cycle corrections). Categorisation of 'perspective' was based on the definitions presented in the Supplementary materials (Section C) and not the authors' description, due to large variability in the definitions of perspectives used in the literature. The type of sensitivity analysis was recorded as per the authors' definition (one-way, two-way, multi-way, probabilistic, scenario or bootstrapping). An analysis was considered a scenario analysis if terms similar to the following were used: "scenario analysis", "structural sensitivity analysis" and/or "tested key/structural assumptions". Uptake was recorded as: "NA", "Assumed 100% uptake rate", "based on revealed data" and "based on observational data".

The justification and testing of modelling techniques were examined, as reported in each study's methods, sensitivity analysis, and discussion sections. The first question was whether the study authors justified their choice of modelling technique. The study authors were considered to have justified their choice if they explained the suitability of their chosen technique or validated their model using a group of experts. The second question was whether the researchers had explored the impact of the modelling technique on their findings within a sensitivity analysis. This would involve creating an alternative model using a different technique. The third question was whether the study provided any discussion of the modelling technique chosen, aiming to determine whether studies discussed their chosen technique's limitations or acknowledged the uncertainty involved. Studies that only discussed modelling limitations in general were not considered to have included modelling techniques in their discussion.

### *Data analysis*

The main analysis involved creating summary statistics (number of studies and percentages) for the following data fields: country, clinical purpose, time horizon, perspective, cost and outcome discount rates, type of economic analysis, modelling technique and justification, uptake methods, inclusion of process and intermediate outcomes and sensitivity analyses. The modelling technique and type of economic analysis were examined by year. A descriptive analysis was conducted to summarise how process or intermediate outcomes had been captured across studies and to contextualise the results.

Summary statistics were also created for the modelling technique and type of sensitivity analysis for each clinical purpose. The results were tabulated, and shading was used to illustrate the proportion of studies in each category, with darker shading indicating a larger proportion. Narrative synthesis was used to investigate the differences in methods across each clinical purpose.

A supplementary analysis was conducted whereby studies evaluating the same genetic/genomic test for the same clinical condition were grouped to facilitate comparison of results. To allow examination of the impact of analytical methods, the criteria were strict; studies with similar but not identical tests or testing sequences were not included in this analysis. Studies were then further classified according to whether the study authors reported the testing as being cost-effective or not.

## Results

The database search yielded 8,223 records published between the 1st of January 2010 and the 15th of June 2022 (**Figure 3**). After removing duplicates, 5,814 records were included in the title/abstract screen. Nineteen additional records were identified through scanning relevant systematic reviews. From the total of 5,833 records, 291 articles were obtained for full text review, and of these 231 met the inclusion criteria. The included studies can be found in **Table 2**, with basic characteristics and references given in the Supplementary materials (Section D). The primary reasons for exclusion at full text review were incorrect intervention (e.g., pathogen testing or gene expression profiling test), incorrect study type (e.g., costing analysis or a trial-based study), and incorrect publication type (e.g., study protocols).

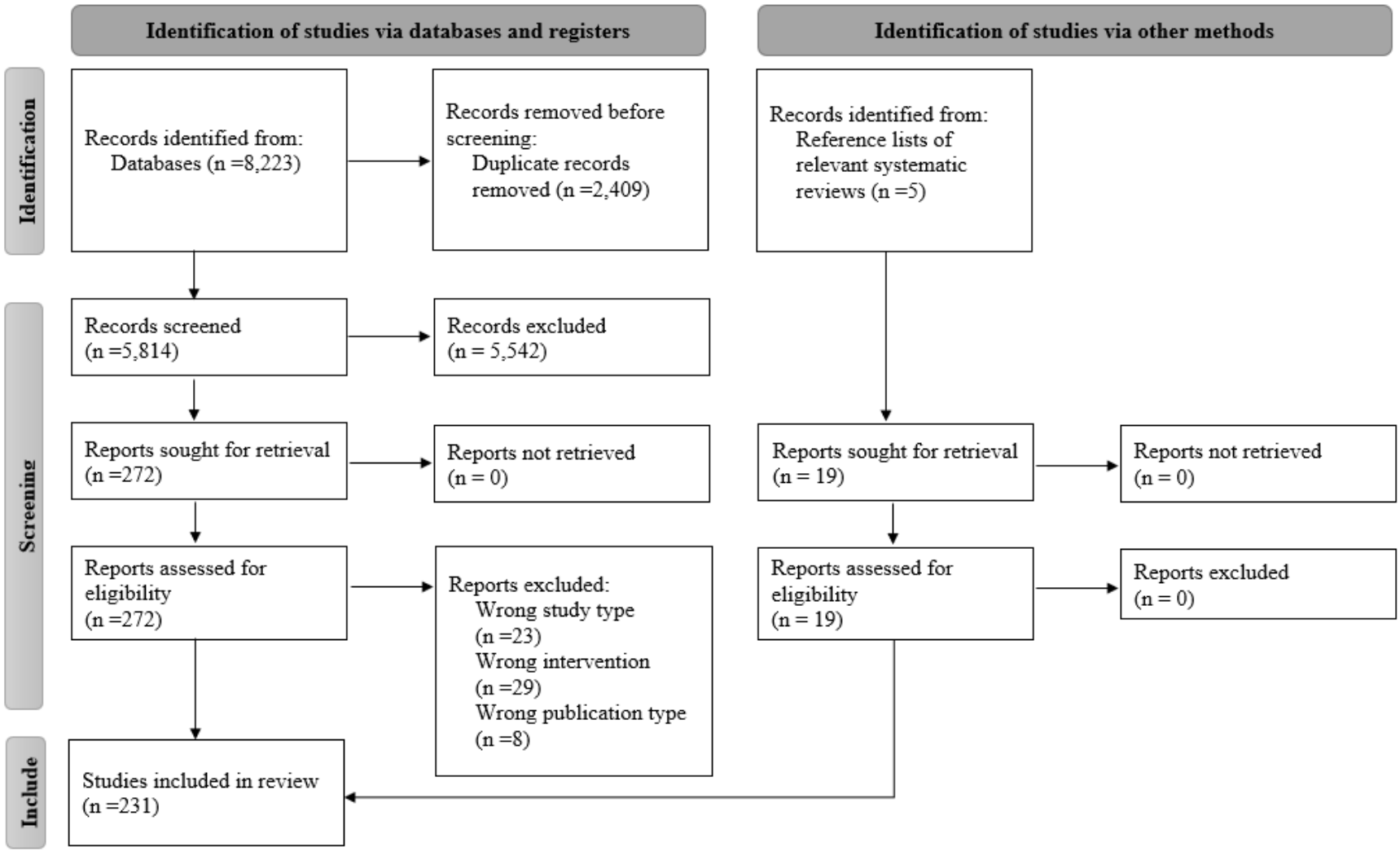


**Figure 3. PRISMA flow diagram.**

**Table 2. Included studies**

| N | Study ID | Title |
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| 1 | Ademi (2014) | Cascade screening based on genetic testing is cost-effective: Evidence for the implementation of models of care for familial hypercholesterolemia |
| 2 | Ademi (2020) | Health economic evaluation of screening and treating children with familial hypercholesterolemia early in life: Many happy returns on investment? |
| 3 | Alagoz (2016) | Cost-effectiveness of one-time genetic testing to minimize lifetime adverse drug reactions |
| 4 | Alkhatib (2018) | Ex ante economic evaluation of genetic testing for the ARG389 beta1-adrenergic receptor polymorphism to support bucindolol treatment decisions in Stage III/iv heart failure |
| 5 | Anh (2021) | First-trimester screening versus non-invasive prenatal testing for Down syndrome at high-risk pregnant women in Hanoi Obstetrics and Gynecology Hospital, Vietnam: A cost-utility analysis |
| 6 | Asphaug (2019) | The cost-effectiveness of multigene panel testing for hereditary breast and ovarian cancer in Norway |
| 7 | Avram (2021) | The cost-effectiveness of genotyping versus sequencing for prenatal cystic fibrosis carrier screening |
| 8 | Ayres (2015) | A cost-effectiveness analysis comparing different strategies to implement noninvasive prenatal testing into a Down syndrome screening program |
| 9 | Azimi (2016) | Carrier screening by next-generation sequencing: Health benefits and cost-effectiveness |
| 10 | Banerjee (2020) | Cost-effectiveness analysis of genetic testing and tailored first-line therapy for patients with metastatic gastrointestinal stromal tumors |
| 11 | Barone (2014) | KRAS early testing: Consensus initiative and cost- effectiveness evaluation for metastatic colorectal patients in an Italian setting |
| 12 | Barzi (2015) | Comparative effectiveness of screening strategies for Lynch syndrome |
| 13 | Bayón (2019) | The consequences of implementing non-invasive prenatal testing with cell-free foetal DNA for the detection of Down syndrome in the Spanish National Health Service: A cost-effectiveness analysis |
| 14 | Behl (2012) | Cost-effectiveness analysis of screening for KRAS and BRAF mutations in metastatic colorectal cancer |
| 15 | Benn (2015) | An economic analysis of cell-free DNA non-invasive prenatal testing in the US general pregnancy population |
| 16 | Bennette (2015) | The cost-effectiveness of returning incidental findings from next-generation genomic sequencing |
| 17 | Beulen (2014) | The consequences of implementing non-invasive prenatal testing in Dutch National Health Care: A cost-effectiveness analysis |

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| 18 | Biltaji (2021) | Can cost-effectiveness analysis inform genotype-guided aspirin use for primary colorectal cancer prevention? |
| 19 | Blank (2011) | KRAS and BRAF mutation analysis in metastatic colorectal cancer: A cost-effectiveness analysis from a Swiss perspective |
| 20 | Brown (2015) | A value-based medicine cost-utility analysis of genetic testing for neovascular macular degeneration |
| 21 | Cai (2021) | cost-effectiveness of CYP2C19 genotyping to guide antiplatelet therapy for acute minor stroke and high risk transient ischemic attack |
| 22 | Catchpool (2019) | A cost-effectiveness model of genetic testing and periodical clinical screening for the evaluation of families with dilated cardiomyopathy |
| 23 | Cenin (2018) | Costs and outcomes of Lynch syndrome screening in the australian colorectal cancer population |
| 24 | Chen (2015) | Cost-effectiveness analysis of alternative screening and treatment strategies for heterozygous familial hypercholesterolemia in the United States |
| 25 | Chen (2016) | Cost-effectiveness analysis of different genetic testing strategies for Lynch syndrome in Taiwan |
| 26 | Choi (2019) | Cost-effectiveness of screening for HLA-B*1502 prior to initiation of carbamazepine in epilepsy patients of Asian ancestry in the United States |
| 27 | Colosi (2017) | First trimester contingent screening for trisomies 21, 18, 13: Is this model cost efficient and feasible in public health system? |
| 28 | Compagni (2013) | Genetic screening for the predisposition to venous thromboembolism: A cost-utility analysis of clinical practice in the Italian health care system |
| 29 | Crawford (2021) | Diagnosing newborns with suspected mitochondrial disorders: An economic evaluation comparing early exome sequencing to current typical care |
| 30 | Cressman (2016) | Economic impact of genomic diagnostics for intermediate-risk acute myeloid leukaemia |
| 31 | Crimmins (2017) | QUAD versus cfdna in an urban population in the second trimester for detection of trisomy 21: A cost sensitivity analysis |
| 32 | Crosland (2018) | Cost-utility analysis of searching electronic health records and cascade testing to identify and diagnose familial hypercholesterolaemia in England and Wales |
| 33 | Cucke (2013) | First trimester contingent screening for trisomies 21, 18, 13: Is this model cost efficient and feasible in public health system? |
| 34 | de Alava (2022) | Cost-effectiveness analysis of molecular diagnosis by next-generation sequencing versus sequential single testing in metastatic non-small cell lung cancer patients from a south Spanish hospital perspective |

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| 35 | de Graaff (2017) | Cost-effectiveness of different population screening strategies for hereditary haemochromatosis in Australia |
| 36 | de Lima Lopes (2012) | Cost-effectiveness of epidermal growth factor receptor mutation testing and first-line treatment with gefitinib for patients with advanced adenocarcinoma of the lung |
| 37 | Dinh (2011) | Health benefits and cost-effectiveness of primary genetic screening for Lynch syndrome in the general population |
| 38 | Dionne (2018) | An initial health economic evaluation of pharmacogenomic testing in patients treated for childhood cancer with anthracyclines |
| 39 | Doble (2017) | Cost-effectiveness of precision medicine in the fourth-line treatment of metastatic lung adenocarcinoma: An early decision analytic model of multiplex targeted sequencing |
| 40 | Dong (2012) | Cost-effectiveness of HLA-B*1502 genotyping in adult patients with newly diagnosed epilepsy in Singapore |
| 41 | Dong (2015) | Cost-effectiveness analysis of genotyping for HLA-B∗5801 and an enhanced safety program in gout patients starting allopurinol in Singapore |
| 42 | Dong (2020) | Cost-effectiveness of multigene pharmacogenetic testing in patients with acute coronary syndrome after percutaneous coronary intervention |
| 43 | Donnan (2011) | A cost-effectiveness analysis of thiopurine methyltransferase testing for guiding 6-mercaptopurine dosing in children with acute lymphoblastic leukemia |
| 44 | Downie (2020) | Exome sequencing for isolated congential hearing loss: A cost-effectiveness analysis |
| 45 | Dragojlovic (2018) | The cost and diagnostic yield of exome sequencing for children with suspected genetic disorders: A benchmarking study |
| 46 | Duplantie (2013) | Cost-effectiveness of the management of Rh-Negative pregnant women |
| 47 | Eccleston (2017) | A cost-effectiveness evaluation of germline BRCA1 and BRCA2 testing in UK women with ovarian cancer |
| 48 | Erten (2016) | Universal versus targeted screening for Lynch syndrome: Comparing ascertainment and costs based on clinical experience |
| 49 | Facadio Antero (2021) | Cost-effectiveness of preimplantation genetic testing for aneuploidy for fresh donor oocyte cycles |
| 50 | Fairbrother (2016) | Prenatal screening for fetal aneuploidies with cell-free DNA in the general pregnancy population: A cost-effectiveness analysis |
| 51 | Fernández (2019) | Diagnostic yield of genetic tests in epilepsy: A meta-analysis and cost-effectiveness study |
| 52 | Folse (2013) | Cost-effectiveness of a genetic test for breast cancer risk |

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| 53 | Foote (2017) | Cost comparison of genetic testing strategies in women with epithelial ovarian cancer |
| 54 | Gallego (2015) | Next-generation sequencing panels for the diagnosis of colorectal cancer and polyposis syndromes: A cost-effectiveness analysis |
| 55 | Gansen (2019) | Lethal privacy: Quantifying life years lost if the right to informational self-determination guides genetic screening for Lynch syndrome |
| 56 | Garfield (2012) | Clinical and cost consequences of incorporating a novel non-invasive prenatal test into the diagnostic pathway for fetal trisomies |
| 57 | Gausachs (2012) | MLH1 promoter hypermethylation in the analytical algorithm of Lynch syndrome: A cost-effectiveness study |
| 58 | Gekas (2011) | Rapid testing versus karyotyping in Down's syndrome screening: Cost-effectiveness and detection of clinically significant chromosome abnormalities |
| 59 | GoodSmith (2019) | The impact of biomarker screening and cascade genetic testing on the cost-effectiveness of MODY genetic testing |
| 60 | Goranitis (2022) | Is faster better? an economic evaluation of rapid and ultra-rapid genomic testing in critically ill infants and children |
| 61 | Gordon (2017) | Noninvasive fetal RhD genotyping of RhD negative pregnant women for targeted anti-d therapy in Australia: A cost-effectiveness analysis |
| 62 | Gould-Suarez (2014) | Cost-effectiveness and diagnostic effectiveness analyses of multiple algorithms for the diagnosis of Lynch syndrome |
| 63 | Goverde (2016) | Cost-effectiveness of routine screening for Lynch syndrome in endometrial cancer patients up to 70 years of age |
| 64 | Greeley (2011) | The cost-effectiveness of personalized genetic medicine: The case of genetic testing in neonatal diabetes |
| 65 | Green (2014) | Economic evaluation of using a genetic test to direct breast cancer chemoprevention in white women with a previous breast biopsy |
| 66 | Guzauskas (2022) | Cost-effectiveness of population-wide genomic screening for Lynch syndrome in the United States |
| 67 | Gyselaers (2015) | Contingent non-invasive prenatal testing: An opportunity to improve non-genetic aspects of fetal aneuploidy screening |
| 68 | Hao (2021) | Economic evaluation of universal Lynch syndrome screening protocols among newly diagnosed patients with colorectal cancer |
| 69 | Hart (2019) | Projected cost-effectiveness for 2 gene-drug pairs using a multigene panel for patients undergoing percutaneous coronary intervention |

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| 70 | Hawk (2013) | Costs and clinical outcomes of noninvasive fetal RhD typing for targeted prophylaxis |
| 71 | Hendrix (2021) | Clarifying the trade-offs of risk-stratified screening for prostate cancer: A cost-effectiveness study |
| 72 | Hopkins (2020) | Cell-free DNA for Down syndrome screening in obese women: Is it a cost-effective strategy? |
| 73 | Hoskins (2019) | Targeted surgical prevention of epithelial ovarian cancer is cost effective and saves money in BRCA mutation carrying family members of women with epithelial ovarian cancer. a canadian model |
| 74 | Howell (2018) | A population-based cost-effectiveness study of early genetic testing in severe epilepsies of infancy |
| 75 | HQO (2019) | Noninvasive prenatal testing for trisomies 21, 18, and 13, sex chromosome aneuploidies, and microdeletions: A health technology assessment |
| 76 | HQO (2020) | Genome-wide sequencing for unexplained developmental disabilities or multiple congenital anomalies: A health technology assessment |
| 77 | HQO (2021) | Multi-gene pharmacogenomic testing that includes decision-support tools to guide medication selection for major depression: A health technology assessment |
| 78 | HQO (2010) | KRAS testing for anti-EGFR therapy in advanced colorectal cancer |
| 79 | HQO (2020) | Cell-free circulating tumour DNA blood testing to detect EGFR T790M mutation in people with advanced non–small cell lung cancer: A health technology assessment |
| 80 | HQO (2022) | Genetic testing for familial hypercholesterolemia: Health technology assessment |
| 81 | Huang (2020) | Prenatal screening for trisomy 21: A comparative performance and cost analysis of different screening strategies |
| 82 | Hurry (2020) | Canadian cost-effectiveness model of brcadriven surgical prevention of breast/ovarian cancers compared to treatment if cancer develops |
| 83 | Incerti (2022) | Cost-effectiveness of genome sequencing for diagnosing patients with undiagnosed rare genetic diseases |
| 84 | Ingles (2012) | A cost-effectiveness model of genetic testing for the evaluation of families with hypertrophic cardiomyopathy |
| 85 | Jackson (2021) | Cost-effectiveness of cascade genetic testing for familial hypercholesterolemia in the United States: A simulation analysis |
| 86 | Jayasinghe (2021) | Cost-effectiveness of targeted exome analysis as a diagnostic test in glomerular diseases |
| 87 | Jutkowitz (2017) | The cost-effectiveness of HLA-B*5801 screening to guide initial urate-lowering therapy for gout in the United States |
| 88 | Kaimal (2015) | Prenatal testing in the genomic age: Clinical outcomes, quality of life, and costs |

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| 89 | Kang (2020) | The predicted impact and cost-effectiveness of systematic testing of people with incident colorectal cancer for Lynch syndrome |
| 90 | Ke (2017) | Cost-effectiveness analysis for genotyping before allopurinol treatment to prevent severe cutaneous adverse drug reactions |
| 91 | Kerr (2017) | cost-effectiveness of cascade testing for familial hypercholesterolaemia, based on data from familial hypercholesterolaemia services in the UK |
| 92 | Kodabuckus (2020) | Exome sequencing for prenatal detection of genetic abnormalities in fetal ultrasound anomalies: An economic evaluation |
| 93 | Kostenko (2019) | Clinical and economic impact of adopting noninvasive prenatal testing as a primary screening method for fetal aneuploidies in the general pregnancy population |
| 94 | Krepline (2021) | Cost-effectiveness analysis of universal germline testing for patients with pancreatic cancer |
| 95 | Kunst (2022) | Population-based newborn screening for germline TP53 variants: Clinical benefits, cost-effectiveness, and value of further research |
| 96 | Kwon (2011) | Testing women with endometrial cancer to detect Lynch syndrome |
| 97 | Kwon (2019) | BRCA mutation testing for first-degree relatives of women with high-grade serous ovarian cancer |
| 98 | Ladabaum (2011) | Strategies to identify the Lynch syndrome among patients with colorectal cancer: A cost-effectiveness analysis |
| 99 | Lala (2013) | Genetic testing in patients with acute coronary syndrome undergoing percutaneous coronary intervention: A cost-effectiveness analysis |
| 100 | Lavelle (2022) | Cost-effectiveness of exome and genome sequencing for children with rare and undiagnosed conditions |
| 101 | Lázaro (2017) | Cost-effectiveness of a cascade screening program for the early detection of familial hypercholesterolemia |
| 102 | Lee (2021) | The cost-effectiveness of preimplantation genetic testing for aneuploidy in the United States: An analysis of cost and birth outcomes from 158, 665 in vitro fertilization cycles |
| 103 | Leenen (2016) | Cost-effectiveness of routine screening for Lynch syndrome in colorectal cancer patients up to 70 years of age |
| 104 | Li (2015) | cost-effectiveness of sequencing 34 cancer-associated genes as an aid for treatment selection in patients with metastatic melanoma |
| 105 | Li (2018) | cost-effectiveness of karyotyping, chromosomal microarray analysis, and targeted next-generation sequencing of patients with unexplained global developmental delay or intellectual disability |

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| 106 | Li (2020) | Cost-effectiveness of genome-wide sequencing for unexplained developmental disabilities and multiple congenital anomalies |
| 107 | Li (2017) | A multigene test could cost-effectively help extend life expectancy for women at risk of hereditary breastcancer |
| 108 | Lim (2018) | Is BRCA mutation testing cost effective for early stage breast cancer patients compared to routine clinical surveillance? the case of an upper middle-income country in Asia |
| 109 | Lipton (2020) | cost-effectiveness of in vitro fertilisation and preimplantation genetic testing to prevent transmission of BRCA1/2 mutations |
| 110 | Little (2010) | The cost-effectiveness of prenatal screening for spinal muscular atrophy |
| 111 | Loong (2022) | Clinical and economic impact of upfront next-generation sequencing for metastatic NSCLC in East Asia |
| 112 | Lu (2016) | Economic analysis of ALK testing and crizotinib therapy for advanced non-small-cell lung cancer |
| 113 | Lu (2018) | Cost-effectiveness of ALK testing and first-line crizotinib therapy for non-small-cell lung cancer in China |
| 114 | Luime (2016) | Cost-effectiveness model for evaluating new diagnostic tests in the evaluation of patients with inflammatory arthritis at risk of having rheumatoid arthritis |
| 115 | Mallow (2021) | Cost-utility analysis of single nucleotide polymorphism panel-based machine learning algorithm to predict risk of opioid use disorder |
| 116 | Manchanda (2015) | Cost-effectiveness of population screening for BRCA mutations in Ashkenazi Jewish women compared with family history-based testing |
| 117 | Manchanda (2017) | Cost-effectiveness of population based BRCA testing with varying Ashkenazi Jewish ancestry |
| 118 | Manchanda (2018) | Cost-effectiveness of population-based BRCA1, BRCA2, RAD51C, RAD51D, BRIP1, PALB2 mutation testing in unselected general population women |
| 119 | Manchanda (2019) | A cost-effectiveness analysis of multigene testing for all patients with breast cancer |
| 120 | Maxwell (2017) | Diagnostic performance and costs of contingent screening models for trisomy 21 incorporating non-invasive prenatal testing |
| 121 | McKay (2018) | Universal screening at age 1–2 years as an adjunct to cascade testing for familial hypercholesterolaemia in the UK: A cost-utility analysis |
| 122 | Michaan (2021) | Preimplantation genetic testing for BRCA gene mutation carriers: A cost-effectiveness analysis |
| 123 | Michaan (2021) | cost-effectiveness of whole population BRCA genetic screening for cancer prevention in Israel |
| 124 | Moise (2019) | Cell free fetal DNA to triage antenatal rhesus immune globulin: Is it really cost-effective in the United States? |

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| 125 | Moretti (2018) | A cost-effectiveness analysis of maternal CYP2D6 genetic testing to guide treatment for postpartum pain and avert infant adverse events |
| 126 | Morris (2014) | Model-based analysis of costs and outcomes of non- invasive prenatal testing for Down's syndrome using cell free fetal DNA in the UK National Health Service |
| 127 | Moya-Alarcón (2019) | Cost–utility analysis of germline BRCA1/2 testing in women with high-grade epithelial ovarian cancer in spain |
| 128 | Müller (2019) | Economic modeling of risk-adapted screen-and-treat strategies in women at high risk for breast or ovarian cancer |
| 129 | Murugappan (2015) | Cost-effectiveness analysis of preimplantation genetic screening and in vitro fertilization versus expectant management in patients with unexplained recurrent pregnancy loss |
| 130 | Mvundura (2010) | The cost-effectiveness of genetic testing strategies for Lynch syndrome among newly diagnosed patients with colorectal cancer |
| 131 | Nadal (2021) | Clinical and economic impact of current ALK rearrangement testing in spain compared with a hypothetical no-testing scenario |
| 132 | Narasimhalu (2020) | cost-effectiveness of genotype-guided antiplatelet therapy in Asian ischemic stroke patients: Ticagrelor as an alternative to clopidogrel in patients with CYP2C19 loss of function mutations |
| 133 | Narita (2015) | Cost-effectiveness analysis of EGFR mutation testing and gefitinib as first-line therapy for non-small cell lung cancer |
| 134 | Naylor (2014) | Cost-effectiveness of MODY genetic testing: Translating genomic advances into practical health applications |
| 135 | Neovius (2015) | Cost-effectiveness of first trimester non-invasive fetal RhD screening for targeted antenatal anti-d prophylaxis in RhD-negative pregnant women: A model-based analysis |
| 136 | Neumann (2020) | An economic analysis of preimplantation genetic testing for aneuploidy by polar body biopsy in advanced maternal age |
| 137 | Neumann (2020) | An economic analysis of aneuploidy screening of oocytes in assisted reproduction in Germany |
| 138 | Neyt (2014) | Introducing the non-invasive prenatal test for trisomy 21 in Belgium: A cost-consequences analysis |
| 139 | Ngeow (2015) | Detecting germline PTEN mutations among at-risk patients with cancer: An age- and sex-specific cost-effectiveness analysis |
| 140 | Nherera (2011) | Probabilistic cost-effectiveness analysis of cascade screening for familial hypercholesterolaemia using alternative diagnostic and identification strategies |
| 141 | Norman (2012) | Cost-effectiveness of carrier screening for cystic fibrosis in Australia |

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| 142 | Norum (2014) | BRCA mutation carrier detection. a model-based cost-effectiveness analysis comparing the traditional family history approach and the testing of all patients with breast cancer |
| 143 | Nshimyumukiza (2014) | cost-effectiveness of newborn screening for cystic fibrosis: A simulation study |
| 144 | Nshimyumukiza (2018) | Cell-free DNA–based non-invasive prenatal screening for common aneuploidies in a canadian province: A cost-effectiveness analysis |
| 145 | O'Brien (2021) | Estimated cost-effectiveness of genetic testing in siblings of newborns with cancer susceptibility gene variants |
| 146 | Ohno (2013) | The role of noninvasive prenatal testing as a diagnostic versus a screening tool - a cost-effectiveness analysis |
| 147 | Ökem (2017) | Economic analysis of prenatal screening strategies for Down syndrome in singleton pregnancies in Turkey |
| 148 | Okere (2018) | An evaluation of the cost-effectiveness of comprehensive MTM integrated with point-of-care phenotypic and genetic testing for u.s. elderly patients after percutaneous coronary intervention |
| 149 | Okun (2014) | The price of performance: A cost and performance analysis of the implementation of cell-free fetal DNA testing for Down syndrome in Ontario, |
| 150 | O'Leary (2013) | Prenatal screening for Down syndrome in Australia: Costs and benefits of current and novel screening strategies |
| 151 | Olgiati (2012) | Should pharmacogenetics be incorporated in major depression treatment? economic evaluation in high- and middle-income European countries |
| 152 | Panattoni (2012) | The cost-effectiveness of genetic testing for CYP2C19 variants to guide thienopyridine treatment in patients with acute coronary syndromes: A New Zealand evaluation |
| 153 | Parthan (2013) | cost-effectiveness of targeted high-dose atorvastatin therapy following genotype testing in patients with acute coronary syndrome |
| 154 | Pastorino (2020) | Cost-effectiveness analysis of genetic diagnostic strategies for Lynch syndrome in Italy |
| 155 | Patel (2014) | Cost-utility analysis of genotype-guided antiplatelet therapy in patients with moderate-to- high risk acute coronary syndrome and planned percutaneous coronary intervention |
| 156 | Patel (2018) | cost-effectiveness of population based BRCA1 founder mutation testing in Sephardi Jewish women |
| 157 | Pelczarska (2018) | The cost-effectiveness of screening strategies for familial hypercholesterolaemia in poland |
| 158 | Pereira (2019) | Cost-utility analysis of genetic polymorphism universal screening in colorectal cancer prevention by detection of high-risk individuals |
| 159 | Perez (2011) | Cost-effectiveness of genetic testing in family members of patients with long-qt syndrome |

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| 160 | Pichereau (2010) | Cost-effectiveness of UGT1A1*28 genotyping in preventing severe neutropenia following FOLFIRI therapy in colorectal cancer |
| 161 | Plumpton (2015) | Cost-effectiveness of screening for hla-a*31:01 prior to initiation of carbamazepine in epilepsy |
| 162 | Ramdzan (2021) | Cost-effectiveness of colorectal cancer genetic testing |
| 163 | Ramos (2018) | cost-effectiveness of the cancer prevention program for carriers of the BRCA1/2 mutation |
| 164 | Rens (2020) | Cost-effectiveness of a pharmacogenomic test for stratified isoniazid dosing in treatment of active tuberculosis |
| 165 | Romanus (2015) | Cost-effectiveness of multiplexed predictive biomarker screening in non-small-cell lung cancer |
| 166 | Saito (2017) | Cost-effectiveness analysis of the use of comprehensive molecular profiling before initiating monoclonal antibody therapy against metastatic colorectal cancer in Japan |
| 167 | Saito (2019) | Cost-effectiveness of BRCA1/2 mutation profiling to target olaparib use in patients with metastatic breast cancer |
| 168 | Salikhanov (2021) | Swiss cost-effectiveness analysis of universal screening for Lynch syndrome of patients with colorectal cancer followed by cascade genetic testing of relatives |
| 169 | Sanford Kobayashi (2022) | Cost efficacy of rapid whole genome sequencing in the pediatric intensive care unit |
| 170 | Saokaew (2014) | Cost-effectiveness analysis of HLA-B*5801 testing in preventing allopurinol-induced sjs/ten in Thai population |
| 171 | Saramago (2018) | High-throughput non-invasive prenatal testing for fetal rhesus d status in RhD-negative women not known to be sensitised to the RhD antigen: A systematic review and economic evaluation |
| 172 | Saramago (2018) | High-throughput, non-invasive prenatal testing for fetal rhesus d genotype to guide antenatal prophylaxis with anti-d immunoglobulin: A cost-effectiveness analysis |
| 173 | Schackman (2013) | Cost-effectiveness analysis of UGT1A1 genetic testing to inform antiretroviral prescribing in HIV disease |
| 174 | Schluckebier (2020) | Cost-effectiveness analysis comparing companion diagnostic tests for EGFR, ALK, and ROS1 versus next-generation sequencing (NGS) in advanced adenocarcinoma lung cancer patients |
| 175 | Schofield (2019) | Long-term economic impacts of exome sequencing for suspected monogenic disorders: Diagnosis, management, and reproductive outcomes |
| 176 | Severin (2015) | Economic evaluation of genetic screening for Lynch syndrome in Germany |
| 177 | Shang (2021) | Introducing the non-invasive prenatal testing for detection of Down syndrome in China: A cost-effectiveness analysis |

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| 178 | Shiffman (2012) | Cost-effectiveness model of use of genetic testing as an aid in assessing the likely benefit of aspirin therapy for primary prevention of cardiovascular disease |
| 179 | Shiroiwa (2010) | Cost-effectiveness analysis of KRAS testing and cetuximab as last-line therapy for colorectal cancer |
| 180 | Sie (2014) | Fourfold increased detection of Lynch syndrome by raising age limit for tumour genetic testing from 50 to 70 years is cost-effective |
| 181 | Simoes Correa-Galendi (2021) | Economic modelling of screen-and-treat strategies for Brazilian women at risk of hereditary breast and ovarian cancer |
| 182 | Simons (2021) | Early cost-effectiveness of whole-genome sequencing as a clinical diagnostic test for patients with inoperable Stage IIIB, C/iv non-squamous non-small-cell lung cancer |
| 183 | Sluiter (2019) | An economic model of the cost-utility of pre-emptive genetic testing to support pharmacotherapy in patients with major depression in primary care |
| 184 | Snowsill (2014) | A systematic review and economic evaluation of diagnostic strategies for Lynch syndrome |
| 185 | Snowsill (2015) | A model-based assessment of the cost-utility of strategies to identify Lynch syndrome in early-onset colorectal cancer patients |
| 186 | Snowsill (2017) | Molecular testing for Lynch syndrome in people with colorectal cancer: Systematic reviews and economic evaluation |
| 187 | Snowsill (2020) | Cost-effectiveness of the Manchester approach to identifying Lynch syndrome in women with endometrial cancer |
| 188 | Somigliana (2019) | Cost-effectiveness of preimplantation genetic testing for aneuploidies |
| 189 | Song (2013) | Clinical utility and cost of non-invasive prenatal testing with cfdna analysis in high-risk women based on a US population |
| 190 | Stark (2017) | Prospective comparison of the cost-effectiveness of clinical whole-exome sequencing with that of usual care overwhelmingly supports early use and reimbursement |
| 191 | Stark (2019) | Does genomic sequencing early in the diagnostic trajectory make a difference? a follow-up study of clinical outcomes and cost-effectiveness |
| 192 | Steuten (2019) | cost-effectiveness of multigene panel sequencing for patients with advanced non–small-cell lung cancer |
| 193 | Su (2021) | Cost-effectiveness of genomic test-directed olaparib for metastatic castration-resistant prostate cancer |
| 194 | Sun (2019) | A cost-effectiveness analysis of multigene testing for all patients with breast cancer |
| 195 | Sun (2022) | Cost-effectiveness of genetic testing for all women diagnosed with breast cancer in China |
| 196 | Sutherland (2019) | Economic evaluation of a novel genetic screening test for risk of venous thromboembolism compared with standard of care in women considering combined hormonal contraception in switzerland |

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| 197 | Szczepura (2011) | A new fetal RhD genotyping test: Costs and benefits of mass testing to target antenatal anti-d prophylaxis in England and Wales |
| 198 | Tan (2020) | Utility of incorporating next-generation sequencing (NGS) in an Asian non-small cell lung cancer (NSCLC) population: Incremental yield of actionable alterations and cost-effectiveness analysis |
| 199 | Tanner (2020) | Cost-effectiveness of combinatorial pharmacogenomic testing for depression from the canadian public payer perspective |
| 200 | Teitelbaum (2015) | Costs and benefits of non-invasive fetal RhD determination |
| 201 | Teng (2020) | Is HLA-B*58:01 genotyping cost effective in guiding allopurinol use in gout patients with chronic kidney disease? |
| 202 | Tsai (2015) | Cost-effectiveness analysis of carrier and prenatal genetic testing for x-linked hemophilia |
| 203 | Tsiplova (2017) | A microcosting and cost-consequence analysis of clinical genomic testing strategies in autism spectrum disorder |
| 204 | Tuffaha (2018) | Cost-effectiveness analysis of germ-line BRCA testing in women with breast cancer and cascade testing in family members of mutation carriers |
| 205 | Vallejo-Torres (2015) | Cost-effectiveness analysis of a national newborn screening program for biotinidase deficiency |
| 206 | Van der Ploeg (2015) | Cost-effectiveness of newborn screening for cystic fibrosis determined with real-life data |
| 207 | Van Nguyen (2017) | Incremental cost-effectiveness of algorithm-driven genetic testing versus no testing for maturity onset diabetes of the young (MODY) in Singapore |
| 208 | Vidavalur (2021) | Economic evaluation of point of care universal newborn screening for glucose-6-phosphate dehydrogenase deficiency in United States |
| 209 | Vijayaraghavan (2012) | Cost-effectiveness of KRAS testing in metastatic colorectal cancer patients in the United States and Germany |
| 210 | Walker (2015) | A cost-effectiveness analysis of first trimester non-invasive prenatal screening for fetal trisomies in the United States |
| 211 | Walker (2014) | A cost-effectiveness analysis of cell free DNA as a replacement for serum screening for Down syndrome |
| 212 | Wanapirak (2019) | Fetal Down syndrome screening models for developing countries; part ii: Cost-benefit analysis |
| 213 | Wang (2012) | Influence of patient preferences on the cost-effectiveness of screening for Lynch syndrome |
| 214 | Wang (2012) | Predictive genetic testing of first degree relatives of mutation carriers is a cost-effective strategy in preventing hereditary nonpolyposis colorectal cancer in Singapore |

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| 215 | Wei (2019) | CYP2D6∗10 pharmacogenetic-guided SERM could be a cost-effective strategy in chinese patients with hormone receptor-positive breast cancer |
| 216 | Wei (2020) | Cost-effectiveness analysis of CYP2D6*10 pharmacogenetic testing to guide the adjuvant endocrine therapy for postmenopausal women with estrogen receptor positive early breast cancer in China |
| 217 | Westwood (2014) | KRAS mutation testing of tumours in adults with metastatic colorectal cancer: A systematic review and cost-effectiveness analysis |
| 218 | Westwood (2014) | Epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation testing in adults with locally advanced or metastatic non-small cell lung cancer: A systematic review and cost-effectiveness analysis |
| 219 | Wong (2021) | cost-effectiveness analysis of a polygenic risk tailored breast cancer screening programme in Singapore |
| 220 | Wordsworth (2010) | DNA testing for hypertrophic cardiomyopathy: A cost-effectiveness model |
| 221 | Wu (2022) | Genomic sequencing for the diagnosis of childhood mitochondrial disorders: a health economic evaluation |
| 222 | Wu (2017) | Cost-effectiveness of osimertinib for EGFR mutation–positive non–small cell lung cancer after progression following first-line EGFR tki therapy |
| 223 | Xie (2020) | Noninvasive prenatal testing for trisomies 21, 18, and 13, sex chromosome aneuploidies, and microdeletions in average-risk pregnancies: A cost-effectiveness analysis |
| 224 | Xu (2019) | Cost-effectiveness analysis of non-invasive prenatal testing for Down syndrome in China |
| 225 | Yuen (2018) | Cost-effectiveness of genome and exome sequencing in children diagnosed with autism spectrum disorder |
| 226 | Yuliwulandari (2021) | Cost-effectiveness analysis of genotyping for HLA-B*15:02 in Indonesian patients with epilepsy using a generic model |
| 227 | Zarca (2020) | Cost-effectiveness analysis of pretreatment screening for NUDT15 defective alleles |
| 228 | Zhang (2019) | Cost-effectiveness of prenatal screening and diagnostic strategies for Down syndrome: A microsimulation modeling analysis |
| 229 | Zhao (2022) | Newborn screening for inherited metabolic diseases using tandem mass spectrometry in China: Outcome and cost–utility analysis |
| 230 | Zhu (2020) | A model-based cost-effectiveness analysis of pharmacogenomic panel testing in cardiovascular disease management: Preemptive, reactive, or none? |
| 231 | Zou (2022) | Diagnostic value and cost-effectiveness of next generation sequencing-based testing for treatment of patients with advanced/metastatic non-squamous non-small cell lung cancer in the US |

### *Study characteristics*

Most studies came from high-income countries, with the largest number of studies from the United States (44%), Canada (12%), the United Kingdom (10%) and Australia (10%). The single largest category of studies was treatment planning (n=82, 35%). This was followed by: genetic testing for risk of cancer (n=57, 25%); identification of congenital anomaly syndrome (n=46, 20%); genetic risk assessment (n=20, 9%); molecular diagnosis of a genetic disorder (n=17, 7%); carrier screening (n=5, 2%) and newborn screening for inborn errors of metabolism (n=4, 2%). Only a few studies in the newborn screening category were identified, which was a result of limiting it to inborn errors of metabolism. All other studies of newborn screening were classified as genetic risk assessment.

### *Key components of the economic evaluation*

The key components of the identified economic models, as detailed in **Table 3**, are summarised below.

#### *Time horizon*

"Lifetime" was the most common time horizon, followed by "1–10 years" and "less than one year". "Other" includes "No time component" and "Not reported", which were common for decision trees where short treatment periods were evaluated.

#### *Perspective*

The most common perspective was health care funder at 87%. Fifteen per cent of studies presented a societal perspective, 6% presented a combined healthcare funder and patient perspective, and 1% presented a patient perspective only.

#### *Discount rate*

Discount rates varied from 0% to 5%. The most common rates applied were 0% and 3% for both costs and outcomes.

**Table 3. Key methodological aspects**

| **Methodological aspects (N=231)** | **Response (n, %)** | | | | | | |
|---|---|---|---|---|---|---|---|
| **Time horizon** | **less than one year** | **1–10 years** | **11–30 years** | **31–50 years** | **Lifetime** | **Other** | |
| | 39, 17% | 53, 23% | 10, 4% | 7, 3% | 110, 48% | 20, 9% | |
| **Perspective** | **Societal** | **Health care funder + patient** | **Health care funder** | **Patient** | | | |
| | 35, 15% | 14, 6% | 200, 87% | 3, *1%* | | | |
| **Cost discount rate** | **None** | **1.50%** | **2%** | **3%** | **3.50%** | **4%** | **5%** |
| | 77, 33% | 6, 3% | 3, 1% | 96, 42% | 26, 11% | 3, 1% | 20, 9% |
| **Outcome discount rate** | **None** | **1.50%** | **2%** | **3%** | **3.50%** | **4%** | **5%** |
| | 85, 37% | 6, 3% | 3, 1% | 86, 26% | 28, 12% | 2, 1% | 21, 9% |
| **Study type** | **CUA** | **CBA** | **CEA** | **CUA and CEA** | **Threshold analysis** | **Cost and consequence** | |
| | 130, 56% | 5, 2% | 118, 51% | 0, 0% | 3, 1% | 14, 6% | |

Abbreviations: CBA, cost-benefit analysis; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; n, number .
Notes: Darker shading indicates a larger proportion of studies in each category.

*Type of analysis*

The most common study types were cost-utility analysis (CUA) and cost-effectiveness analysis (CEA) (56% and 51% respectively). From 2010 to 2022, the percentage of CUA per year ranged from 36% to 61% and the percentage of CEA ranged from 27% to 63%. The first cost-benefit analysis (CBA) was performed in 2019, and their number increased over time (0% in 2010 to 11% in 2022). No cost-minimisation studies were identified

*Sensitivity analysis*

The types of sensitivity analyses identified can be found in **Table 4**. Most studies involved one-way deterministic (81%) and/or probabilistic sensitivity analyses (59%). A large minority of studies (38%) involved scenario analyses. These sensitivity analysis methods were the predominant approaches across all clinical purposes.

**Table 4. Type of sensitivity analysis presented within studies by clinical purpose**

| Sensitivity analysis (N=231) | Treatment planning | | Identification of congenital anomaly syndrome | | Molecular diagnosis of genetic disorder | | Genetic testing for risk of cancer | | Newborn screening for inborn errors of metabolism | | Carrier screening | | Genetic risk assessment | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| One-way deterministic | 72 | 88% | 27 | 59% | 13 | 76% | 48 | 84% | 2 | 50% | 5 | 100% | 19 | 95% | 186 | 81% |
| Probabilistic | 59 | 72% | 13 | 28% | 12 | 71% | 36 | 63% | 2 | 50% | 3 | 60% | 12 | 60% | 137 | 59% |
| Scenario | 33 | 40% | 13 | 28% | 9 | 53% | 21 | 37% | 2 | 50% | 0 | 0% | 10 | 50% | 88 | 38% |
| Two-way deterministic | 8 | 10% | 4 | 9% | 0 | 0% | 1 | 2% | 0 | 0% | 0 | 0% | 2 | 10% | 15 | 6% |
| Bootstrapping | 0 | 0% | 2 | 4% | 0 | 0% | 1 | 2% | 0 | 0% | 0 | 0% | 0 | 0% | 3 | 1% |
| Multi-way deterministic | 1 | 1% | 3 | 7% | 1 | 6% | 0 | 0% | 1 | 25% | 0 | 0% | 1 | 5% | 7 | 3% |

Abbreviations: n; number.
Notes: Darker shading indicates a larger proportion of studies in each category.

### *Inclusion of intermediate and process outcomes*

Three per cent of studies (n=7) included the impacts of intermediate and process outcomes in their evaluations.[19-26] Four studies used willingness to pay (WTP) estimates from discrete choice experiments (DCEs), which included process and intermediate attributes.[19 20, 21, 25] All four studies were classified as involving molecular diagnosis of testing and were conducted between 2020 and 2022. Three of the four studies used the WTP estimates within a CBA;[20, 21, 25] the other study used the WTP estimates as a cost-effectiveness threshold within a CEA.[19]

Three studies relied on estimates from time-trade off studies to capture process and intermediate outcomes, which were used within a CUA.[23, 24, 27] Two of the three studies explored genetic testing for risk of cancer and used estimates from the same time-trade off study, which aimed to capture the psychological impacts of testing.[24, 27] The third study explored the identification of a congenital anomaly and incorporated utilities that aimed to capture the psychological impact of receiving false positive and inconclusive results.[23]

### *Estimation of uptake rates*

Fifty-four per cent of studies did not consider the uptake rate. Twelve per cent of studies assumed a 100% uptake rate. Thirty-four per cent of studies used revealed preference data to estimate the uptake rate, and 3% used stated preference data.

### *Modelling techniques*

The different modelling techniques identified can be found in **Table 5** and are also visually represented in **Figure 4**. Across clinical purposes, decision trees (48%), Markov models (36%), and microsimulations (13%) were the most common modelling techniques. From 2010 to 2020, the annual proportions of decision trees and Markov models per year remained relatively constant (ranging from 30% to 60% and 28% to 50% respectively), while the proportion of microsimulations increased from 0% to 20%. Only one system dynamic model was identified.[28]

**Table 5. Modelling technique by clinical purpose**

| Modelling technique | Treatment planning | | Congenital anomaly syndrome | | Molecular diagnosis of genetic disorder | | Genetic testing for risk of cancer | | Inborn errors of metabolism | | Carrier screening | | Genetic risk | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| Decision tree | 32 | 39% | 35 | 76% | 11 | 65% | 18 | 32% | 3 | 75% | 5 | 100% | 6 | 30% | 110 | 48% |
| Markov model | 39 | 48% | 4 | 9% | 4 | 24% | 23 | 40% | 1 | 25% | 0 | 0% | 13 | 65% | 84 | 36% |
| Microsimulation | 9 | 11% | 5 | 11% | 2 | 12% | 12 | 21% | 0 | 0% | 0 | 0% | 1 | 5% | 29 | 13% |
| Discrete event simulation | 0 | 0% | 2 | 4% | 2 | 12% | 3 | 5% | 0 | 0% | 0 | 0% | 0 | 0% | 7 | 3% |
| Partition survival analysis | 2 | 2% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 2 | 1% |
| System dynamics model | 0 | 0% | 0 | 0% | 0 | 0% | 1 | 2% | 0 | 0% | 0 | 0% | 0 | 0% | 1 | 0% |
| Dynamic transmission model | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% |

Abbreviations: n; number.

Darker shading indicates a larger proportion of studies in each category.

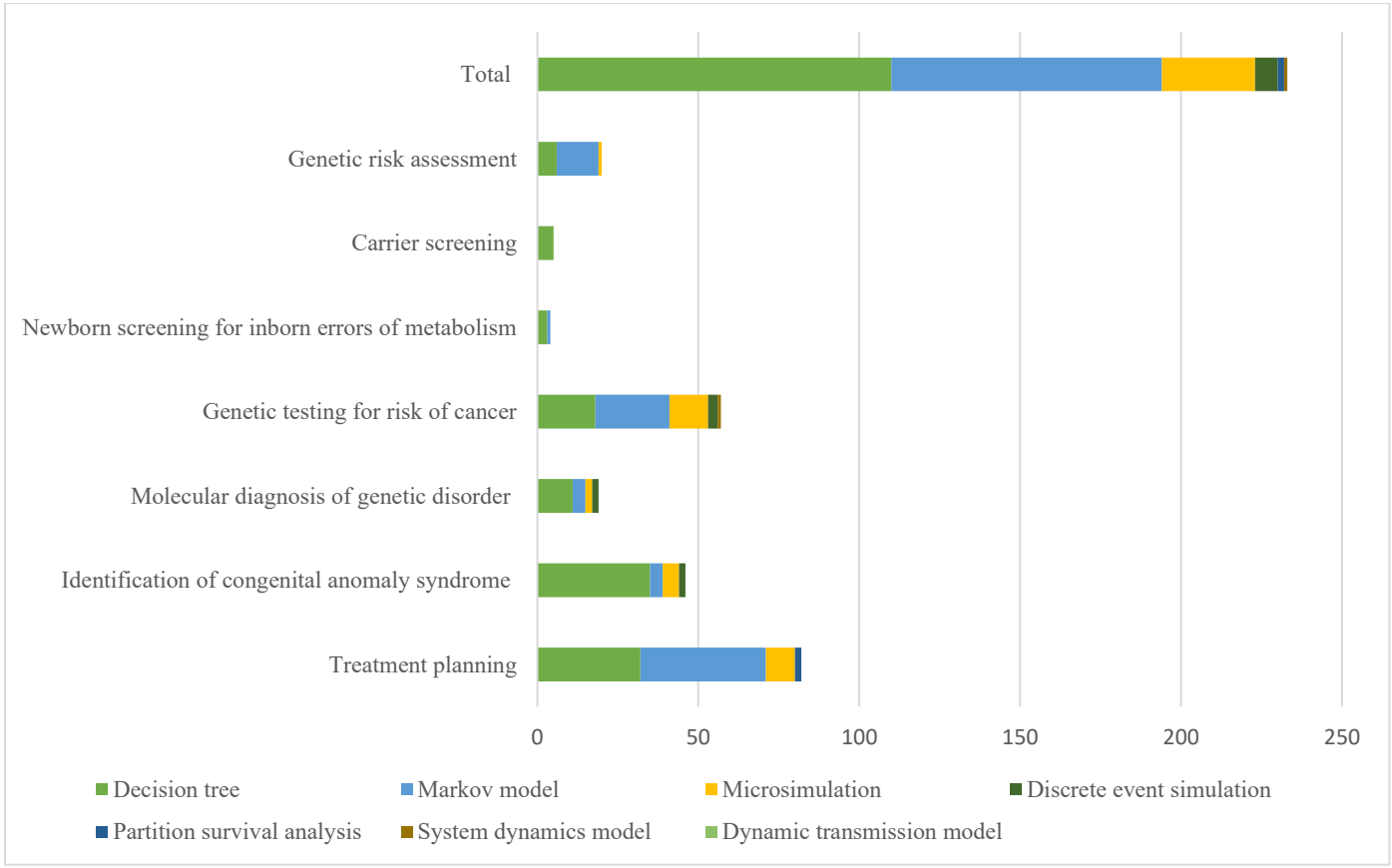


**Figure 4. Modelling technique by clinical purpose**

### *Justification and testing of modelling techniques*

The number of studies that presented some justification or testing of the modelling technique was extremely low. Twelve per cent of studies provided some form of justification for their modelling technique. One per cent of studies tested the impact of the modelling technique in a sensitivity analysis. Within the discussion, 5% of studies included the limitations of their specific modelling technique or made a comparison to studies using a different approach.

### *Comparison of results*

A total of 88 studies, covering 21 conditions/tests, were identified for comparisons between studies evaluating the same genetic/genomic test for the same clinical condition (**Table 6**). The number of studies for each clinical condition/test ranged from 2 to 16, with 2 being the most common. The greatest number of studies were found for NIPT for T21 (n=16, 63% similar). The results from these studies ranged from cost saving to USD1,278,330 per T21 case detected.[29, 30] The percentage of studies with similar results ranged from 50% to 100%. The following groups had 50% of studies with similar results: HLA-B*5801 testing for gout (n= 4), EGFR testing for non-small cell lung cancer (n=2), NIPT for T21, T18, T13, sex chromosome aneuploidies and microdeletions (n=2), and WES and WGS for developmental disabilities and multiple congenital anomalies (n=2).

**Table 6. Comparison of results for studies evaluating the same genetic/genomic test for the same clinical condition**

| Population (category) | Clinical condition/Phenotype | Test | N | Number with consistent cost-effectiveness results | % with consistent cost-effectiveness findings[1] |
|---|---|---|---|---|---|
| **Treatment planning** | | | | | |
| Asymptomatic fetus | RhD-negative pregnant women | High-throughput non-invasive prenatal testing | 9 | 5 | 56% |
| Symptomatic adult | Acute Coronary Syndrome | CYP2C19 genetic testing | 4 | 3 | 75% |
| | Breast cancer | CYP2D6*10 genetic testing | 2 | 2 | 100% |
| | Colorectal cancer | KRAS testing | 5 | 4 | 80% |
| | Epilepsy | HLA-B*1502 genotyping | 3 | 2 | 67% |
| | Gout | HLA-B*5801 testing | 4 | 2 | 50% |
| | Non-small cell lung cancer | NGS panel (10 actionable markers) | 2 | 1 | 50% |
| **Identification of a congenital anomaly** | | | | | |
| Pre-implantation embryo | Women undergoing IVF | Pre-implantation genetic testing | 7 | 1 | 86% |
| Asymptomatic fetus | T21 | NIPT | 16 | 11 | 69% |
| | T21, T18, and T13 | NIPT | 6 | 5 | 83% |
| | T21, T18, and T13 sex chromosome aneuploidies, and microdeletions | NIPT | 2 | 1 | 50% |
| Symptomatic child | Developmental disabilities and multiple congenital anomalies | Whole exome and whole genome sequencing | 2 | 1 | 50% |
| | Suspected monogenic disorders | Exome sequencing | 6 | 2 | 67% |

| | | | | | |
|---|---|---|---|---|---|
| **Molecular diagnosis of a genetic disorder** | | | | | |
| Symptomatic child | Autism spectrum disorder | Whole exome sequencing | 2 | 1 | 50% |
| | Critically ill paediatric patients | Whole genome sequencing | 3 | 3 | 100% |
| **Genetic risk of cancer** | | | | | |
| Pre-implantation embryo | Breast cancer | IVF and pre-implantation genetic testing for BRCA mutations (+/- aneuploidies) | 8 | 6 | 75% |
| | Ovarian or breast cancer | BRCA1/2 testing | 3 | 3 | 100% |
| Symptomatic adult | Breast cancer | BRCA 1/2 testing | 2 | 2 | 100% |
| | Lynch syndrome (Colorectal cancer) | IHC (MMR genes), gene sequencing (4 MMR genes), MSI testing, BRAF V600E mutation testing | 9 | 7 | 78% |
| | | Gene sequencing (4 MMR genes) | 3 | 2 | 67% |
| **Genetic risk assessment** | | | | | |
| Asymptomatic adult | Hypertrophic cardiomyopathy | DNA cascade testing (13 genes) | 2 | 2 | 100% |
| Symptomatic | Familial hypercholesterolaemia | DNA cascade testing (LDLR, APOB, and PCSK9) | 7 | 6 | 86% |

Abbreviations: APOB, Apolipoprotein B; BRCA, Breast cancer gene; CYP2C19/CYP2D6, Cytochrome P450 enzyme genes; DNA, deoxyribonucleic acid; HLA, Human leukocyte antigen; HT, high-throughput; IHC, immunohistochemistry; IVF, in vitro fertilization; LDLR, Low-density lipoprotein receptor; MMR, mismatch repair; MSI, microsatellite instability; n, number; NGS, Next-generation sequencing; NIPT, non-invasive prenatal testing; PCSK9, Proprotein convertase subtilisin/kexin type 9; T13, Trisomy 13; T18, Trisomy 18; T21, Trisomy 21.RetryClaude can make mistakes. Please double-check responses.

Notes: The percentage of studies with consistent cost-effectiveness findings for each condition and test was determined by calculating the proportion of studies that reached the same conclusion (either cost-effective or not, as reported by the study authors).

### *Quality assessment*

Most studies (92%) were assessed as good quality; the remaining studies were average quality, and no studies were assessed as poor quality. A summary of the assessment for each checklist item is shown in **Figure 5**. Decrements in quality were mainly in the item referring to "Presentation and discussion of study results contain all issues of concern for users?" due to authors not acknowledging the modelling technique as a source of uncertainty. This was followed by "Comprehensive description of alternatives" due to the study not giving an indication of the type of genetic/genomic testing undertaken. Other common contributors to lower quality were not applying discounting despite the modelled time horizon being longer than one year and not providing justification for this approach, not presenting an incremental analysis, and not reporting the base year for cost values.

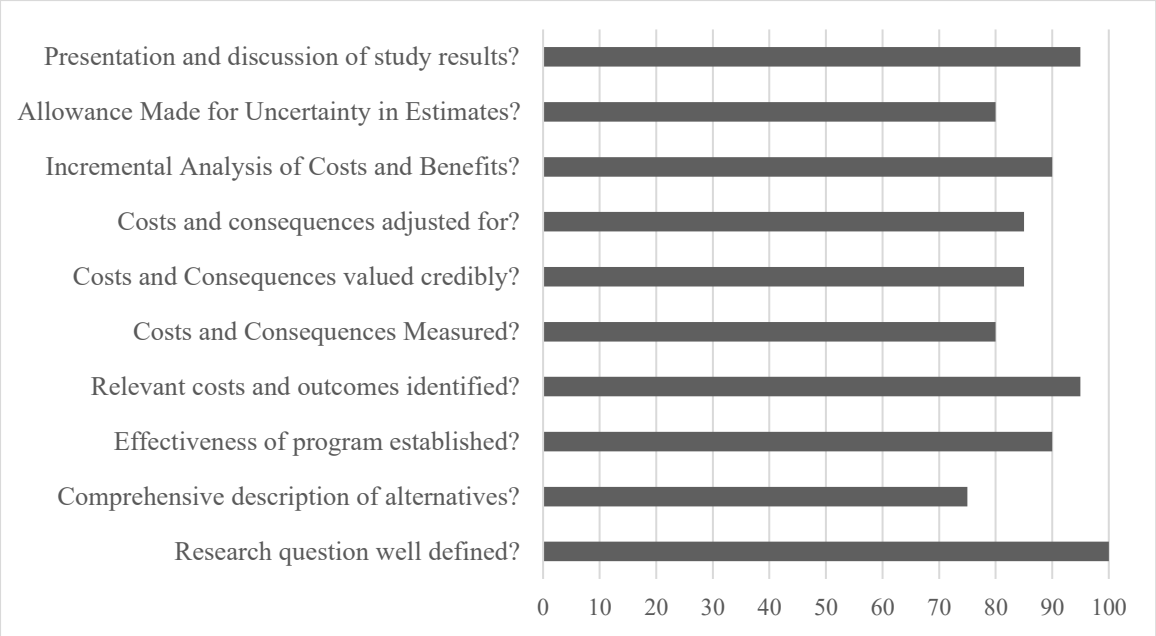


**Figure 5. Summary of economic evaluation quality assessment items for the 231 included studies.**

The shading represents the percentage of studies that met each assessment criterion.

## Discussion

This is the first review to identify primary economic evidence across all clinical conditions and testing purposes within genetic and genomic testing, summarising data from 231 studies. This marks a significant expansion from previous reviews, which included 15–55 studies.[5, 8, 11, 12, 31-33] Most of the included evaluations originated in high-income countries, and were performed in the areas of treatment planning, genetic testing for risk of cancer, and identification of a congenital anomaly. Considerable heterogeneity was observed across studies with respect to key components of the economic evaluations. In general, the choice of time horizon, discount rate and type of economic analysis were justified using guidelines from national funding bodies in the study's respective country. It was common practice to address methodological and parameter uncertainty, with model functional form (i.e., "structural" uncertainties) addressed less frequently.

Phillips et al.[5] identified complex model structures as a key challenge in evaluations of NGS tests.[5, 34] Nonetheless, in the current evidence base, the simplest modelling techniques (decision trees and Markov models) dominated. These results align with previous reviews of genetic and genomic testing that focused on NGS technology, diagnostics, precision oncology and specific clinical conditions.[11, 12, 31-33] However, the current review identified a growing proportion of microsimulations, and one system dynamic model,[28] a technique that was not identified in previous reviews. Given a recent review has suggested system dynamic modelling better captures the complexity of genomic evaluations (precision medicine in particular),[35, 36] it will be interesting to observe whether its usage increases.[35, 36]

The proportion of studies that provided justification for their choice of modelling technique or considered the impact of this choice was very low. The lack of justification is surprising given it is requested by multiple national funding bodies.[3, 37, 38] These results are in line with a previous review focusing on NGS technology, which calls out the large number of studies that did not adhere to reporting guidelines, particularly with respect to the modelling technique.[12] Two studies identified within our review used a scenario analysis to test the impacts of modelling techniques;[20, 25] they presented a decision tree and a discrete event simulation and found the mean cost savings per child

differed by USD7,000 and AUD6,000 (approx. USD3,960) respectively. Looking at the wider literature, studies in breast cancer treatment have explored the impact of different model structures (including modelling technique and number of health states) and found substantial differences in results.[39-41] The choice of modelling technique may alter the outcomes of an evaluation, and it is not clear if the widespread use of (unjustified) simple modelling techniques is appropriate given the complexity of genetic/genomic testing and its consequences.

The second challenge Phillips et al.[5] identified was measuring costs and outcomes, and this was not explicitly addressed in any of the included studies.[5] Most of the studies reviewed here conducted a CUA and valued outcomes using quality-adjusted life years (QALYs) or employed natural units within a CEA. The current gold standard is to value outcomes using QALYs.[3] However, it has been argued that QALYs do not capture the full benefits of genomic testing.[42] Seven studies attempted to include intermediate and/or process outcomes within their evaluations. Interestingly, since 2020, all studies incorporating these outcomes obtained WTP estimates from DCEs for use in a CBA. This contrasts to previous reviews, which did not find any studies attempting to include the broader outcomes of testing,[11,12] and one review that identified a single study that applied a disutility for the psychological impacts of testing within a CUA.[32] Further, a review of recent funding applications for genetic/genomic testing for heritable conditions in Australia found that not one application included psychological impacts.[43] DCEs have been recommended to value the broad range of outcomes associated with genetic and genomic testing, but there is a lack of guidance on whether or how these results should be incorporated into economic evaluations.[12, 44]

To extend the review by Phillips et al.,[5] this study aimed to examine the potential impact of methodological and structural choices on study findings. Due to the small number of studies evaluating the same clinical condition and test, it was difficult to determine the extent to which cost-effectiveness results varied. NIPT for T21 was the area with the largest number of studies identified. These studies demonstrate that models evaluating the same condition and test can have different findings ranging from cost saving to USD1,278,330 per T21 case detected.[29, 30] Supporting these results, a systematic review of NIPT found evaluation results differed based on implementing NIPT as

a first or second line test. Authors of studies included in that review reported challenges with selecting appropriate outcome measures and determining their values.[45] Our analysis revealed that many studies reported a test as being cost-effective when only one specific scenario met an ICER threshold and/or an internationally high ICER threshold was used (e.g., USD100,000). The conclusions of the included studies should be interpreted with caution, considering the methodology used and the results, particularly in sponsored studies.

Advancements are occurring in economic evaluations of genetic and genomic testing. To build on this progress, we recommend further research to develop solutions to incorporate the broader outcomes of testing within CUAs and/or assess the feasibility of shifting towards CBAs. The literature contains little consideration of the impact of different modelling techniques. Of course, in most circumstances it is not feasible to conduct a full exploration of uncertainty through a scenario analysis. Instead, model developers should be encouraged to consider and justify their choices and to discuss their possible impacts on the modelled results. Lastly, research is needed to evaluate the impact of structural and methodological choices on the findings of evaluations within the area of genetic and genomic testing.

### *Quality assessment*

Decrements in quality were mainly in the following item: "Presentation and discussion of study results contain all issues of concern for users?" This is a subjective item and relates directly to the purpose of the current paper. Studies lost points when they failed to acknowledge that the modelling technique was an area of potential uncertainty. This may not have been the case if the quality assessment was performed by a different researcher. To encourage authors to discuss modelling techniques as an area of uncertainty, it could be added as a specific checklist item.

An additional aspect arising from this research was the high level of inadequate reporting of the details of the genetic or genomic testing being evaluated. The absence of these details makes it difficult to identify studies of similar tests, and to have confidence in the costs applied for these tests in the economic models. Many studies reported the genes that caused the disease of interest but did not clearly state the nature of testing or the specific gene variants tested. Further, many studies used

the terms “whole genome sequencing” or “whole exome sequencing” when they were in fact evaluating a targeted exome test.

### *Limitations*

This paper describes a broad approach to enable the collection and summary of a high volume of data, which had both strengths and limitations. A thorough formal literature search was conducted, identifying more than 8,000 records. A grey literature search was not deemed feasible, meaning studies from other sources may have been missed. The analysis of results must be interpreted with caution: different cost-effectiveness thresholds exist, and comparisons have been made across countries and contexts. All newborn screening studies were categorised as genetic risk assessment, when in fact they are considered differently within the literature. However, recategorisation of these studies would not have changed the key findings. The review also relied on the study authors’ assessment of the test’s cost-effectiveness. Similarly, the type of sensitivity analysis used by study authors was not examined in detail. Categorisation was dependent on the authors’ terms, and their definitions may have differed. The model structure was only examined in terms of the modelling technique, despite other structural differences.[46] Lastly, the quality assessment was limited to the Drummond checklist. Although the more detailed Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist was considered,[47] the Drummond checklist was chosen given the large number of included studies and its ability to provide an overall indication of quality. Using the Drummond checklist identifies how well the study addressed the minimum reporting requirements but does not identify any underlying weaknesses in the model structure.

## Conclusions

This review summarises the current health economic evidence base for economic models in genetic and genomic testing. This information will help health economists to understand the full spectrum of the approaches that have been taken, and to contextualise the results of individual studies. Complex model structures and measuring costs and outcomes have been identified as key challenges in economic evaluations of genetic/genomic testing, and solutions remain underdeveloped. In terms of the model structure, decision trees and Markov models were the most commonly used techniques, with a trend toward microsimulations aimed at capturing the complexities of testing, though few studies justified their chosen technique. It is important that authors justify their choices and explicitly consider the possible impact of structural uncertainty. In terms of measuring outcomes, while a small number of researchers made progress in attempting to include intermediate and process outcomes in their evaluations, further guidance is needed on whether and how to incorporate these aspects. The extent to which cost-effectiveness results varied for evaluations of the same clinical condition and test was difficult to establish. Future research is needed to evaluate the impact of structural and methodological choices on the findings of evaluations within the area of genetic and genomic testing.

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## Supplementary materials

### Section A. Search terms

**Table 7. EMBASE search terms**

| No. | Query |
|---|---|
| 1 | high throughput sequencing'/exp OR 'high throughput sequenc*':ti,ab,kw OR 'next generation sequenc*':ti,ab,kw,de OR 'next-generation sequenc*':ti,ab,kw,de OR ngs:ti,ab,kw,de OR 'non-invasive prenatal test*':ti,kw,ab,de OR 'non invasive prenatal test*':ti,kw,de,ab OR nipt:ti,kw,de,ab OR 'noninvasive prenatal test*':ti,ab,de,kw OR metagenomic$:ti,ab,kw,de OR wgs:ti,ab,kw,de OR wes:ti,ab,kw,de OR germline:ti,ab,kw,de OR inherited:ti,ab,kw,de OR inheritable:ti,ab,kw,de OR 'genomic test*':ti,ab,kw,de OR 'gene* test*':ti,ab,kw,de |
| 2 | (('massive* parallel' OR panel OR deep OR 'whole genome' OR exome OR multigene OR 'multi gene' OR monogenic) NEAR/5 (sequenc* OR test*)):ti,ab,kw,de |
| 3 | #1 OR #2 |
| 4 | economic*:ti OR cost*:ti OR utilit*:ti OR 'quality adjusted life year:ti' OR qaly:ti OR 'life year saved':ti OR icer:ti OR value:ti OR hta:ti OR 'health technology assessment':ti OR markov:ti OR 'decision tree':ti OR 'outcome assessment':ti OR 'decision analy*':ti OR 'decision-analy*':ti OR 'cea':ti |
| 5 | #3 AND #4 |
| 6 | #5 NOT (('animal'/exp OR 'nonhuman'/exp OR 'rodent'/exp OR 'animal experiment'/exp OR 'experimental animal'/exp OR rat:ti,ab OR rats:ti,ab OR mouse:ti,ab OR mice:ti,ab OR dog$:ti,ab OR pig$:ti,ab OR porcine:ti,ab OR swine:ti,ab OR chick$:ti,ab) NOT 'human'/exp) AND [2010-2022]/py |
| 7 | #6 NOT ([conference abstract]/lim OR [conference review]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [book]/lim OR 'case report'/de) AND [english]/lim |

**Table 8. MEDLINE search terms**

| No. | Query |
|---|---|
| 1 | High-Throughput Nucleotide Sequencing/ or high throughput sequenc*.mp. or next generation sequenc*.mp. or next-generation sequenc*.mp. or ngs.mp. or non-invasive prenatal test*.mp. or non invasive prenatal test*.mp. or nipt.mp. or noninvasive prenatal test*.mp. or metagenomic$.mp. or wgs.mp. or wes.mp. or germline.mp. or inherited.mp. or inheritable.mp. or genomic test*.mp. or gene* test*.mp. |
| 2 | ((massively parallel or panel or whole genome or exome or multigene or multi gene or monogenic) and (sequenc* or test*)).mp. |
| 3 | 1 or 2 |
| 4 | economic*.ti. or cost*.ti. or utilit*.ti. or quality adjusted life year.ti. or qaly.ti. or life year saved.ti. or icer.ti. or value.ti. or hta.ti. or health technology assessment.ti. or markov.ti. or decision tree.ti. or outcome assessment.ti. or decision analy*.ti. or decision-analy*.ti. or cea.ti. |
| 5 | 3 and 4 |
| 6 | limit 5 to (humans and yr="2010 - 2022") |

**Table 9. SCOPUS search terms**

| No. | Query |
|---|---|
| 1 | TITLE( "high throughput sequenc*" OR "next generation sequenc*" OR ngs OR "non invasive prenatal test*" OR nipt OR "noninvasive prenatal test*" OR metagenomic$ OR wgs OR wes ) OR (TITLE((germline OR inherited OR inheritable OR gene* OR genomic OR "massively parallel" OR panel OR "whole genome" OR exome OR multigene OR "multi gene" OR monogenic) AND (sequenc* OR test*))) AND ( TITLE ( economic* OR cost* OR utilit* ) ) AND ( LIMIT-TO ( PUBYEAR,2022) OR ( LIMIT-TO ( PUBYEAR,2021) OR LIMIT-TO ( PUBYEAR,2020) OR LIMIT-TO ( PUBYEAR,2019) OR LIMIT-TO ( PUBYEAR,2018) OR LIMIT-TO ( PUBYEAR,2017) OR LIMIT-TO ( PUBYEAR,2016) OR LIMIT-TO ( PUBYEAR,2015) OR LIMIT-TO ( PUBYEAR,2014) OR LIMIT-TO ( PUBYEAR,2013) OR LIMIT-TO ( PUBYEAR,2012) OR LIMIT-TO ( PUBYEAR,2011) OR LIMIT-TO ( PUBYEAR,2010) ) AND ( LIMIT-TO ( LANGUAGE,"English" ) ) |

**Table 10. ECON LIT search terms**

| No. | Query |
|---|---|
| 1 | TI(Sequencing) OR TI(sequence analysis) OR TI(genomics) OR TI(genomic testing) OR TI(gene testing) OR AB(Sequencing) OR AB(sequence analysis) OR AB(genomics) OR AB(genomic testing) OR AB(gene testing)<br>Limits: 2010-2022 |

## Section B. Eligibility criteria

**Table 11. Screening inclusion and exclusion criteria**

| Item | Inclusion criteria | Exclusion criteria |
|---|---|---|
| Population | All populations | |
| Intervention | Untargeted whole genome and exome sequencing | Gene expression profiling |
| | Large scale gene analysis (>200 genes) | Pathogen testing |
| | Medium gene panels (11-200 gene) | |
| | Small gene panels (2-10 genes) | |
| | Monogenic | |
| Comparator | Any comparator | |
| Outcomes | All health outcomes | |
| Study types | Cost-effectiveness analysis | Conference abstracts |
| | Cost-benefit analysis | Protocols |
| | Cost-utility analysis | Costing analysis |
| | Cost minimisation analysis | Budget impact analysis |
| | Cost and consequence analysis | |
| | Threshold analysis | |
| Study language | English language articles only | |
| Publication date | From 1 January 2010 - present | |
| Exclusions | Non-human studies | |

## Section C. Data extraction

**Table 12. Data extraction fields**

| Aspect | Category |
|---|---|
| Basic characteristics | Title |
| | Country |
| | Objective |
| Methodological aspects | Time horizon |
| | Perspective |
| | Cost discount rates |
| | Outcome discount rate |
| | Type of economic analysis |
| | How is ICER expressed |
| | Costing year |
| Population and testing | Clinical condition/phenotype |
| | Size of modelling population (n) |
| | Purpose of testing (categorised) |
| | Initial population to be tested (categorised) |
| | Test |
| | Scale of gene analysis |
| | Add on/replacement? |
| | Supplementary testing |
| | Current practice |
| | Other comparators |
| | Cascade testing |
| | Sequence of intervention |
| | Sequence of current practice |
| | Patient attributes |
| Model structure | Modelling technique |
| | Justification for modelling technique in methods? |
| | Sensitivity analysis method |
| | Tested modelling techniques in sensitivity analysis? |
| | Was modelling technique included in discussion? |
| Results | Cost-effective? |
| | ICER |
| | ICER threshold |
| | Other results |
| | Conclusion |

Abbreviations: ICER; incremental cost-effectiveness ratio, n; number

**Table 13. Economic evaluation perspectives**

| Perspective | Meaning | Notes |
|---|---|---|
| Societal | Medical and non-medical costs included | |
| Health care funder | Government and/or health insurance medical costs | Payer perspective e.g. US - Medicare, Medicaid |
| Healthcare funder + patient | Government, health insurer and patient health costs | |
| Patient | Patient health costs | |

## Section D. Included studies

**Table 14. Included studies, with references**

| Reference ID | Title | Time horizon | Perspective | Cost discount rates | Outcome discount rate | Type of economic analysis |
|---|---|---|---|---|---|---|
| Ademi (2014)[48] | Cascade screening based on genetic testing is cost-effective: Evidence for the implementation of models of care for familial hypercholesterolemia | 10 years | Health care funder | 5.0% | 5.0% | Cost-utility and cost-effectiveness |
| Ademi (2020)[49] | Health economic evaluation of screening and treating children with familial hypercholesterolemia early in life: Many happy returns on investment? | Lifetime | Health care funder | 5.0% | 5.0% | Cost-utility and cost-effectiveness |
| Alagoz (2016)[50] | Cost-effectiveness of one-time genetic testing to minimize lifetime adverse drug reactions | Lifetime | Health care funder | 3.0% | 3.0% | Cost-utility and cost-effectiveness |
| Alkhatib (2018)[51] | Ex ante economic evaluation of genetic testing for the ARG389 beta1-adrenergic receptor polymorphism to support bucindolol treatment decisions in Stage III/IV heart failure | 18 months | Health care funder | 3.0% | 3.0% | Cost-utility and cost-effectiveness |
| Anh (2021)[52] | First-trimester screening versus non-invasive prenatal testing for Down syndrome at high-risk pregnant women in Hanoi Obstetrics and Gynecology Hospital, Vietnam: A cost-utility analysis | Pregnancy until birth | Societal | None | None | Cost-utility and cost-effectiveness |
| Asphaug (2019)[53] | The cost-effectiveness of multigene panel testing for hereditary breast and ovarian cancer in Norway | Lifetime | Health care funder | 4.0% | 4.0% | Cost-utility |

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|---|---|---|---|---|---|---|
| Avram (2021)[54] | The cost-effectiveness of genotyping versus sequencing for prenatal cystic fibrosis carrier screening | Lifetime | Societal | 3.0% | 3.0% | Cost-utility |
| Ayres (2015)[55] | A cost-effectiveness analysis comparing different strategies to implement noninvasive prenatal testing into a Down syndrome screening program | Pregnancy to birth | Health care funder + patient | None | None | Cost-effectiveness |
| Azimi (2016)[56] | Carrier screening by next-generation sequencing: Health benefits and cost effectiveness | Lifetime | Health care funder | 3.0% | 3.0% | Cost-effectiveness |
| Banerjee (2020)[57] | Cost-effectiveness analysis of genetic testing and tailored first-line therapy for patients with metastatic gastrointestinal stromal tumors | 10 years | Health care funder | 3.0% | 3.0% | Cost-utility |
| Barone (2014)[58] | KRAS early testing: Consensus initiative and cost-effectiveness evaluation for metastatic colorectal patients in an Italian setting | NR | NR | None | None | Cost-utility |
| Barzi (2015)[59] | Comparative effectiveness of screening strategies for Lynch syndrome | Lifetime | Societal | None | None | Cost-effectiveness |
| Bayón (2019)[30] | The consequences of implementing non-invasive prenatal testing with cell-free foetal DNA for the detection of Down syndrome in the Spanish National Health Service: A cost-effectiveness analysis | Pregnancy to birth | Health care funder | None | None | Cost-effectiveness |
| Behl (2012)[60] | Cost-effectiveness analysis of screening for KRAS and BRAF mutations in metastatic colorectal cancer | 10 years | Health care funder | 3.0% | 3.0% | Cost-effectiveness |
| Benn (2015)[61] | An economic analysis of cell-free DNA non-invasive prenatal testing in the US general pregnancy population | Lifetime | Health care funder + patient | None | None | Threshold analysis |

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|---|---|---|---|---|---|---|
| Bennette (2015)[62] | The cost-effectiveness of returning incidental findings from next-generation genomic sequencing | Lifetime | Health care funder | 3.0% | 3.0% | Cost-utility |
| Beulen (2014)[63] | The consequences of implementing non-invasive prenatal testing in Dutch National Health Care: A cost-effectiveness analysis | 10 weeks gestation to birth | Health care funder + patient | None | None | Cost-effectiveness |
| Biltaji (2021)[64] | Can cost-effectiveness analysis inform genotype-guided aspirin use for primary colorectal cancer prevention? | Lifetime | Health care funder | 3.0% | 3.0% | Cost-utility |
| Blank (2011)[65] | KRAS and BRAF mutation analysis in metastatic colorectal cancer: A cost-effectiveness analysis from a Swiss perspective | Lifetime | Health care funder | 3.0% | 3.0% | Cost-utility |
| Brown (2015)[66] | A value-based medicine cost-utility analysis of genetic testing for neovascular macular degeneration | Lifetime | Societal | 3.0% | 3.0% | Cost-utility |
| Cai (2021)[67] | Cost effectiveness of CYP2C19 genotyping to guide antiplatelet therapy for acute minor stroke and high risk transient ischemic attack | Lifetime | Health care funder | 3.0% | 3.0% | Cost-utility |
| Catchpool (2019)[68] | A cost-effectiveness model of genetic testing and periodical clinical screening for the evaluation of families with dilated cardiomyopathy | Lifetime | Health care funder | 5.0% | 5.0% | Cost-utility |
| Cenin (2018)[69] | Costs and outcomes of Lynch syndrome screening in the Australian colorectal cancer population | 1 year | Health care funder | None | None | Cost-effectiveness |
| Chen (2015)[70] | Cost-effectiveness analysis of alternative screening and treatment strategies for heterozygous familial hypercholesterolemia in the United States | Lifetime | Health care funder | 3.0% | 3.0% | Cost-utility |

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|---|---|---|---|---|---|---|
| Chen (2016)[71] | Cost-effectiveness analysis of different genetic testing strategies for Lynch syndrome in Taiwan | Lifetime | Health care funder | 3.0% | 3.0% | Cost-effectiveness |
| Choi (2019)[72] | Cost-effectiveness of screening for HLA-B1502 prior to initiation of carbamazepine in epilepsy patients of Asian ancestry in the United States | Lifetime | Health care funder | 3.0% | 3.0% | Cost-utility |
| Colosi (2017)[73] | First trimester contingent screening for trisomies 21,18,13: Is this model cost efficient and feasible in public health system? | Pregnancy to birth | Healthcare funder | None | None | Cost and consequence |
| Compagni (2013)[74] | Genetic screening for the predisposition to venous thromboembolism: A cost-utility analysis of clinical practice in the Italian health care system | 10 years | Health care funder | 3.0% | 3.0% | Cost-utility |
| Crawford (2021)[75] | Diagnosing newborns with suspected mitochondrial disorders: An economic evaluation comparing early exome sequencing to current typical care | Lifetime | Societal and health care funder | 3.0% | 3.0% | Cost-utility |
| Cressman (2016)[76] | Economic impact of genomic diagnostics for intermediate-risk acute myeloid leukaemia | 10 years | Health care funder | 3.0% | 3.0% | Cost-utility |
| Crimmins (2017)[77] | QUAD versus cfDNA in an urban population in the second trimester for detection of trisomy 21: A cost sensitivity analysis | Pregnancy to birth | Health care funder + patient | None | None | Threshold analysis |
| Crosland (2018)[26] | Cost-utility analysis of searching electronic health records and cascade testing to identify and diagnose familial hypercholesterolaemia in England and Wales | Lifetime | Health care funder + patient | 3.5% | 3.5% | Cost-utility and cost-effectiveness |
| Cuckle (2013)[78] | Cost-effectiveness analysis of molecular diagnosis by next-generation sequencing versus sequential single testing in metastatic non-small cell lung cancer | Pregnancy to birth | Healthcare funder | None | None | Cost and consequence |

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|---|---|---|---|---|---|---|
| | patients from a South Spanish hospital perspective | | | | | |
| de Alava (2022)[79] | Cost-effectiveness of different population screening strategies for hereditary haemochromatosis in Australia | Lifetime | Health care funder | 3.0% | 3.0% | Cost-utility and cost-effectiveness |
| de Graaff (2017)[80] | Cost-effectiveness of epidermal growth factor receptor mutation testing and first-line treatment with gefitinib for patients with advanced adenocarcinoma of the lung | Lifetime | Health care funder | 5.0% | 5.0% | Cost-utility |
| de Lima Lopes (2012)[81] | Health benefits and cost-effectiveness of primary genetic screening for Lynch syndrome in the general population | Lifetime (short surivival) | Health care funder | None | None | Cost-utility |
| Dinh (2011)[82] | An initial health economic evaluation of pharmacogenomic testing in patients treated for childhood cancer with anthracyclines | Lifetime | Health care funder | 3.0% | 3.0% | Cost-utility |
| Dionne (2018)[83] | Cost-effectiveness of precision medicine in the fourth-line treatment of metastatic lung adenocarcinoma: An early decision analytic model of multiplex targeted sequencing | Lifetime | Health care funder | 3.5% | 3.5% | Cost and consequence |
| Doble (2017)[84] | Cost-effectiveness of HLA-B1502 genotyping in adult patients with newly diagnosed epilepsy in Singapore | 10 years | Health care funder | 5.0% | 5.0% | Cost-utility and cost-effectiveness |
| Dong (2012)[85] | Cost-effectiveness analysis of genotyping for HLA-B5801 and an enhanced safety program in gout patients starting allopurinol in Singapore | 8 years | Health care funder | 3.0% | 3.0% | Cost-utility |

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|---|---|---|---|---|---|---|
| Dong (2015)[86] | Cost-effectiveness of multigene pharmacogenetic testing in patients with acute coronary syndrome after percutaneous coronary intervention | Lifetime | Health care funder | 3.0% | 3.0% | Cost-utility |
| Dong (2020)[87] | A cost effectiveness analysis of thiopurine methyltransferase testing for guiding 6-mercaptopurine dosing in children with acute lymphoblastic leukemia | 12 months, 24 months and Lifetime | Health care funder | 3.0% | 3.0% | Cost-utility |
| Donnan (2011)[88] | Exome sequencing for isolated congential hearing loss: A cost-effectiveness analysis | 3 months | Health care funder | None | None | Cost-effectiveness |
| Downie (2020)[19] | The cost and diagnostic yield of exome sequencing for children with suspected genetic disorders: A benchmarking study | 18 years | Health care funder | 5.0% | None | Cost-benefit and cost-effectiveness |
| Dragojlovic (2018)[89] | Cost-effectiveness of the management of Rh-negative pregnant women | NR | Health care funder | None | None | Cost and consequence |
| Duplantie (2013)[90] | A cost-effectiveness evaluation of germline BRCA1 and BRCA2 testing in UK women with ovarian cancer | Less than one year | Health care funder | None | None | Cost-effectiveness |
| Eccleston (2017)[91] | Universal versus targeted screening for Lynch syndrome: Comparing ascertainment and costs based on clinical experience | 50 years | Health care funder | 3.5% | 3.5% | Cost-utility |
| Erten (2016)[28] | Cost-effectiveness of preimplantation genetic testing for aneuploidy for fresh donor oocyte cycles | 5 years | Health care funder + patient | None | None | Cost and consequence |
| Facadio Antero (2021)[92] | Prenatal screening for fetal aneuploidies with cell-free DNA in the general pregnancy population: A cost-effectiveness analysis | Treatment until birth | Health care funder | None | None | Cost-effectiveness |

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|---|---|---|---|---|---|---|
| Fairbrother (2016)[93] | Diagnostic yield of genetic tests in epilepsy: A meta-analysis and cost-effectiveness study | Pregnancy to birth | Health care funder + patient | None | None | Threshold analysis |
| Fernández (2019)[94] | Cost-effectiveness of a genetic test for breast cancer risk | testing period | Patient | None | None | Cost-effectiveness |
| Folse (2013)[95] | Cost comparison of genetic testing strategies in women with epithelial ovarian cancer | Lifetime | Health care funder | 3.0% | 3.0% | Cost-utility |
| Foote (2017)[96] | Next-generation sequencing panels for the diagnosis of colorectal cancer and polyposis syndromes: A cost-effectiveness analysis | NR | Health care funder | None | None | Cost-effectiveness |
| Gallego (2015)[97] | Lethal privacy: Quantifying life years lost if the right to informational self-determination guides genetic screening for Lynch syndrome | Lifetime | Health care funder | 3.0% | None | Cost-utility and cost-effectiveness |
| Gansen (2019)[98] | Clinical and cost consequences of incorporating a novel non-invasive prenatal test into the diagnostic pathway for fetal trisomies | Lifetime | Health care funder | None | None | Cost-effectiveness |
| Garfield (2012)[99] | MLH1 promoter hypermethylation in the analytical algorithm of Lynch syndrome: A cost-effectiveness study | Pregnancy to birth | Health care funder | None | None | Cost and consequence |
| Gausachs (2012)[100] | Rapid testing versus karyotyping in Down syndrome screening: Cost-effectiveness and detection of clinically significant chromosome abnormalities | NR | Health care funder | None | None | Cost-effectiveness |
| Gekas (2011)[101] | The impact of biomarker screening and cascade genetic testing on the cost-effectiveness of MODY genetic testing | Pregnancy to birth | Health care funder | None | None | Cost-effectiveness |

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|---|---|---|---|---|---|---|
| GoodSmith (2019)[102] | Is faster better? An economic evaluation of rapid and ultra-rapid genomic testing in critically ill infants and children | 30 years | Health care funder | 3.0% | 3.0% | Cost-utility |
| Goranitis (2022)[20] | Noninvasive fetal RHD genotyping of RhD negative pregnant women for targeted anti-D therapy in Australia: A cost-effectiveness analysis | Treatment period | Health care funder | None | None | Cost-benefit |
| Gordon (2017)[103] | Cost-effectiveness and diagnostic effectiveness analyses of multiple algorithms for the diagnosis of Lynch syndrome | Pregnancy to birth | Health care funder | None | None | Cost-effectiveness |
| Gould-Suarez (2014)[104] | Cost-effectiveness of routine screening for Lynch syndrome in endometrial cancer patients up to 70 years of age | NR | Health care funder + patient | None | None | Cost-effectiveness |
| Goverde (2016)[105] | The cost-effectiveness of personalized genetic medicine: The case of genetic testing in neonatal diabetes | Lifetime benefits, one year costs | Health care funder | 3.0% | 3.0% | Cost-effectiveness |
| Greeley (2011)[106] | Economic evaluation of using a genetic test to direct breast cancer chemoprevention in white women with a previous breast biopsy | 30 years | Societal | 3.0% | 3.0% | Cost-utility |
| Green (2014)[107] | Cost-effectiveness of population-wide genomic screening for Lynch syndrome in the United States | Lifetime | Health care funder | 3.0% | 3.0% | Cost-utility and cost-effectiveness |
| Guzauskas (2022)[27] | Contingent non-invasive prenatal testing: An opportunity to improve non-genetic aspects of fetal aneuploidy screening | lifetime | Health care funder | 3.0% | 3.0% | Cost-utility and cost-effectiveness |

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| Gyselaers (2015)[108] | Economic evaluation of universal Lynch syndrome screening protocols among newly diagnosed patients with colorectal cancer | Pregnancy to birth | Health care funder | None | None | Cost and consequence |
| Hao (2021)[109] | Projected cost-effectiveness for 2 gene-drug pairs using a multigene panel for patients undergoing percutaneous coronary intervention | NR | Health care funder | None | None | Cost-effectiveness |
| Hart (2019)[110] | Costs and clinical outcomes of noninvasive fetal RhD typing for targeted prophylaxis | 15 months | Health care funder | 3.0% | 3.0% | Cost-utility |
| Hawk (2013)[111] | Clarifying the trade-offs of risk-stratified screening for prostate cancer: A cost-effectiveness study | NR | Health care funder | None | None | Cost and consequence |
| Hendrix (2021)[112] | Cell-free DNA for Down syndrome screening in obese women: Is it a cost-effective strategy? | Lifetime | Health care funder | 3.0% | 3.0% | Cost-utility |
| Hopkins (2020)[113] | Targeted surgical prevention of epithelial ovarian cancer is cost effective and saves money in BRCA mutation carrying family members of women with epithelial ovarian cancer: A Canadian model | Pregnancy to birth | Health care funder | None | None | Cost and consequence |
| Hoskins (2019)[114] | A population-based cost-effectiveness study of early genetic testing in severe epilepsies of infancy | Lifetime | Health care funder | 1.5% | 1.5% | Cost-effectiveness |
| Howell (2018)[115] | Noninvasive prenatal testing for trisomies 21, 18, and 13, sex chromosome aneuploidies, and microdeletions: A health technology assessment | NR | Health care funder | None | None | Cost-effectiveness |

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| HQO (2019)[116] | Genome-wide sequencing for unexplained developmental disabilities or multiple congenital anomalies: A health technology assessment | Pregnancy to birth | Health care funder | None | None | Cost-effectiveness |
| HQO (2020a)[117] | Multi-gene pharmacogenomic testing that includes decision-support tools to guide medication selection for major depression: A health technology assessment | 3 years | Health care funder | None | 1.5% | Cost-effectiveness |
| HQO (2021)[118] | KRAS testing for anti-EGFR therapy in advanced colorectal cancer | 1, 3 and 5 years | Societal and health care funder | None | None | Cost-utility |
| HQO (2010)[119] | Cell-free circulating tumour DNA blood testing to detect EGFR T790M mutation in people with advanced non-small cell lung cancer: A health technology assessment | Lifetime | Health care funder | 5.0% | 5.0% | Cost-utility |
| HQO (2020b)[120] | Genetic testing for familial hypercholesterolemia: Health technology assessment | 10 years | Health care funder | 1.5% | 1.5% | Cost-utility and cost-effectiveness |
| HQO (2022)[121] | Prenatal screening for trisomy 21: A comparative performance and cost analysis of different screening strategies | Lifetime | Health care funder | 1.5% | 1.5% | Cost-utility |
| Huang (2020)[122] | Canadian cost-effectiveness model of BRCA driven surgical prevention of breast/ovarian cancers compared to treatment if cancer develops | Pregnancy to birth | Health care funder | None | None | Cost-effectiveness |
| Hurry (2020)[123] | Cost-effectiveness of genome sequencing for diagnosing patients with undiagnosed rare genetic diseases | 50 years | Health care funder | 1.5% | 1.5% | Cost-utility |
| Incerti (2022)[124] | A cost-effectiveness model of genetic testing for the evaluation of families with hypertrophic cardiomyopathy | 5 years (infants); 15 years (children) | Health care funder | None | None | Cost-effectiveness |
| Ingles (2012)[125] | Cost-effectiveness of cascade genetic testing for familial hypercholesterolemia | Lifetime | Health care funder | 5.0% | 5.0% | Cost-effectiveness |

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| | in the United States: A simulation analysis | | | | | |
| Jackson (2021)[126] | Cost-effectiveness of targeted exome analysis as a diagnostic test in glomerular diseases | 30 and 40 years | Health care funder | 3.0% | 3.0% | Cost-effectiveness |
| Jayasinghe (2021)[127] | The cost-effectiveness of HLA-B*5801 screening to guide initial urate-lowering therapy for gout in the United States | 12 months | Health care funder | None | None | Cost-benefit and cost-effectiveness |
| Jutkowitz (2017)[128] | Prenatal testing in the genomic age: Clinical outcomes, quality of life, and costs | Lifetime | Health care funder | 3.0% | 3.0% | Cost-utility |
| Kaimal (2015)[23] | The predicted impact and cost-effectiveness of systematic testing of people with incident colorectal cancer for Lynch syndrome | Lifetime and until birth separately | Health care funder | 3.0% | 3.0% | Cost-utility |
| Kang (2020)[129] | Cost-effectiveness analysis for genotyping before allopurinol treatment to prevent severe cutaneous adverse drug reactions | Lifetime | Health care funder | 5.0% | 5.0% | Cost-effectiveness |
| Ke (2017)[130] | Cost effectiveness of cascade testing for familial hypercholesterolaemia, based on data from familial hypercholesterolaemia services in the UK | 1 year | Health care funder | None | None | Cost-utility |
| Kerr (2017)[131] | Exome sequencing for prenatal detection of genetic abnormalities in fetal ultrasound anomalies: An economic evaluation | Lifetime | Health care funder | 3.5% | 3.5% | Cost-utility and cost-effectiveness |
| Kodabuckus (2020)[132] | Clinical and economic impact of adopting noninvasive prenatal testing as a primary screening method for fetal aneuploidies in the general pregnancy population | NR | Health care funder | None | None | Cost-effectiveness |
| Kostenko (2019)[133] | Cost-effectiveness analysis of universal germline testing for patients with pancreatic cancer | Pregnancy to birth | Health care funder | None | None | Cost-effectiveness |

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| Krepline (2021)[134] | Population-based newborn screening for germline TP53 variants: Clinical benefits, cost-effectiveness, and value of further research | Lifetime (short survival) | Health care funder | None | None | Cost-effectiveness |
| Kunst (2022)[135] | Testing women with endometrial cancer to detect Lynch syndrome | Lifetime | Societal | 3.0% | 3.0% | Cost-effectiveness |
| Kwon (2011)[136] | BRCA mutation testing for first-degree relatives of women with high-grade serous ovarian cancer | Lifetime | Health care funder + patient | 3.0% | 3.0% | Cost-effectiveness |
| Kwon (2019)[137] | Strategies to identify the Lynch syndrome among patients with colorectal cancer: A cost-effectiveness analysis | 50 years | Health care funder | 3.0% | 5.0% | Cost-utility |
| Ladabaum (2011)[138] | Genetic testing in patients with acute coronary syndrome undergoing percutaneous coronary intervention: A cost-effectiveness analysis | Lifetime | Health care funder | 3.0% | 3.0% | Cost-effectiveness |
| Lala (2013)[139] | Cost-effectiveness of exome and genome sequencing for children with rare and undiagnosed conditions | 10 years | Health care funder | 3.0% | 3.0% | Cost-utility |
| Lavelle (2022)[140] | Cost-effectiveness of a cascade screening program for the early detection of familial hypercholesterolemia | 10 years and lifetime | Health care funder and healthcare funder + patient | 3.0% | 3.0% | Cost-utility and cost-effectiveness |
| Lázaro (2017)[141] | The cost-effectiveness of preimplantation genetic testing for aneuploidy in the United States: An analysis of cost and birth outcomes from 158,665 in vitro fertilization cycles | 10 years | Societal and health care funder | 3.0% | 3.0% | Cost-utility and cost-effectiveness |
| Lee (2021)[142] | Cost-effectiveness of routine screening for Lynch syndrome in colorectal cancer patients up to 70 years of age | IVF until live birth, or 12 months | Health care funder + patient | None | None | Cost-effectiveness |
| Leenen (2016)[143] | Cost effectiveness of sequencing 34 cancer-associated genes as an aid for treatment selection in patients with metastatic melanoma | NR | Health care funder | None | None | Cost-effectiveness |

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| Li (2015)[144] | Cost effectiveness of karyotyping, chromosomal microarray analysis, and targeted next-generation sequencing of patients with unexplained global developmental delay or intellectual disability | 2 years | Health care funder | 3.0% | 3.0% | Cost-utility |
| Li (2018)[145] | Cost-effectiveness of genome-wide sequencing for unexplained developmental disabilities and multiple congenital anomalies | 1 year | Health care funder | None | None | Cost-effectiveness |
| Li (2020)[146] | A multigene test could cost-effectively help extend life expectancy for women at risk of hereditary breast cancer | 3 years | Health care funder | 1.5% | 1.5% | Cost-effectiveness |
| Li (2018)[147] | Is BRCA mutation testing cost effective for early stage breast cancer patients compared to routine clinical surveillance? The case of an upper middle-income country in Asia | Lifetime | Health care funder | 3.0% | 3.0% | Cost-utility and cost-effectiveness |
| Lim (2018)[148] | Cost effectiveness of in vitro fertilisation and preimplantation genetic testing to prevent transmission of BRCA1/2 mutations | Lifetime | Health care funder | 3.0% | 3.0% | Cost-utility and cost-effectiveness |
| Lipton (2020)[149] | The cost-effectiveness of prenatal screening for spinal muscular atrophy | Lifetime | Health care funder | 1.5% | 1.5% | Cost-utility |
| Little (2010)[150] | Clinical and economic impact of upfront next-generation sequencing for metastatic NSCLC in East Asia | Lifetime | Societal | 3.0% | 3.0% | Cost-utility and cost-effectiveness |
| Loong (2022)[151] | Economic analysis of ALK testing and crizotinib therapy for advanced non-small-cell lung cancer | NR | Health care funder | None | None | Cost and consequence |
| Lu (2016)[152] | Cost-effectiveness of ALK testing and first-line crizotinib therapy for non-small-cell lung cancer in China | 10 years | Health care funder | 5.0% | 5.0% | Cost-utility |

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| Lu (2018)[153] | Cost-effectiveness model for evaluating new diagnostic tests in the evaluation of patients with inflammatory arthritis at risk of having rheumatoid arthritis | 10 years | Health care funder | 5.0% | 5.0% | Cost-utility |
| Luime (2016)[154] | Cost-utility analysis of single nucleotide polymorphism panel-based machine learning algorithm to predict risk of opioid use disorder | 1 year | Societal | None | None | Cost-utility |
| Mallow (2021)[155] | Cost-effectiveness of population screening for BRCA mutations in Ashkenazi Jewish women compared with family history-based testing | 5 years | Societal and health care funder | 3.0% | 3.0% | Cost-utility |
| Manchanda (2015)[156] | Cost-effectiveness of population based BRCA testing with varying Ashkenazi Jewish ancestry | Lifetime | Health care funder | 3.5% | 3.5% | Cost-utility |
| Manchanda (2017)[157] | Cost-effectiveness of population-based BRCA1, BRCA2, RAD51C, RAD51D, BRIP1, PALB2 mutation testing in unselected general population women | Lifetime | Health care funder | 3.5% | 3.5% | Cost-utility |
| Manchanda (2018)[158] | A cost-effectiveness analysis of multigene testing for all patients with breast cancer | Lifetime | Health care funder | 3.5% | 3.5% | Cost-utility |
| Manchanda (2019)[159] | Diagnostic performance and costs of contingent screening models for trisomy 21 incorporating non-invasive prenatal testing | Lifetime | Societal and health care funder | 3.5% | 3.5% | Cost-utility and cost-effectiveness |
| Maxwell (2017)[160] | Universal screening at age 1-2 years as an adjunct to cascade testing for familial hypercholesterolaemia in the UK: A cost-utility analysis | Pregnancy to birth | Health care funder | None | None | Cost-effectiveness |
| McKay (2018)[161] | Preimplantation genetic testing for BRCA gene mutation carriers: A cost effectiveness analysis | Lifetime | Health care funder | 3.5% | 3.5% | Cost-utility |
| Michaan (2021)[162] | Cost effectiveness of whole population BRCA genetic screening for cancer prevention in Israel | Lifetime | Health care funder | 3.0% | None | Cost-utility |

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| Michaan (2021a)[163] | Cell free fetal DNA to triage antenatal rhesus immune globulin: Is it really cost-effective in the United States? | Lifetime | Health care funder | 3.0% | None | Cost-utility |
| Moise (2019)[164] | A cost-effectiveness analysis of maternal CYP2D6 genetic testing to guide treatment for postpartum pain and avert infant adverse events | NR | Health care funder | None | None | Cost-effectiveness |
| Moretti (2018)[165] | Model-based analysis of costs and outcomes of non-invasive prenatal testing for Down syndrome using cell free fetal DNA in the UK National Health Service | NR | Societal and health care funder | None | None | Cost-effectiveness |
| Morris (2014)[166] | Cost-utility analysis of germline BRCA1/2 testing in women with high-grade epithelial ovarian cancer in Spain | Pregnancy to birth | Health care funder | None | None | Cost and consequence |
| Moya-Alarcón (2019)[167] | Economic modeling of risk-adapted screen-and-treat strategies in women at high risk for breast or ovarian cancer | 50 years | Health care funder + patient | 3.0% | None | Cost-utility |
| Müller (2019)[168] | Cost-effectiveness analysis of preimplantation genetic screening and in vitro fertilization versus expectant management in patients with unexplained recurrent pregnancy loss | Lifetime | Health care funder | 3.0% | 3.0% | Cost-utility and cost-effectiveness |
| Murugappan (2015)[169] | The cost-effectiveness of genetic testing strategies for Lynch syndrome among newly diagnosed patients with colorectal cancer | IVF treatment to birth | Health care funder + patient | None | None | Cost-effectiveness |
| Mvundura (2010)[170] | Clinical and economic impact of current ALK rearrangement testing in Spain compared with a hypothetical no-testing scenario | Lifetime | Health care funder | 3.0% | 3.0% | Cost-effectiveness |
| Nadal (2021)[171] | Cost effectiveness of genotype-guided antiplatelet therapy in Asian ischemic stroke patients: Ticagrelor as an | Lifetime | Health care funder | 3.0% | 3.0% | Cost-utility and cost-effectiveness |

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| | alternative to clopidogrel in patients with CYP2C19 loss of function mutations | | | | | |
| Narasimhalu (2020)[172] | Cost-effectiveness analysis of EGFR mutation testing and gefitinib as first-line therapy for non-small cell lung cancer | Lifetime | Health care funder | 3.0% | 3.0% | Cost-utility |
| Narita (2015)[173] | Cost-effectiveness of MODY genetic testing: Translating genomic advances into practical health applications | Lifetime | Health care funder | 2.0% | 2.0% | Cost-utility |
| Naylor (2014)[174] | Cost-effectiveness of first trimester non-invasive fetal RHD screening for targeted antenatal anti-D prophylaxis in RhD-negative pregnant women: A model-based analysis | Lifetime | Health care funder | 3.0% | 3.0% | Cost-utility |
| Neovius 2015[175] | An economic analysis of preimplantation genetic testing for aneuploidy by polar body biopsy in advanced maternal age | Pregnancy to birth | Health care funder | 3.0% | 3.0% | Cost-effectiveness |
| Neumann (2020)[176] | An economic analysis of aneuploidy screening of oocytes in assisted reproduction in Germany | 12 months | Health care funder | None | None | Cost-effectiveness |
| Neumann (2020a)[177] | Introducing the non-invasive prenatal test for trisomy 21 in Belgium: A cost-consequences analysis | Treatment until birth | Health care funder | None | None | Cost-effectiveness |
| Neyt (2014)[178] | Detecting germline PTEN mutations among at-risk patients with cancer: An age- and sex-specific cost-effectiveness analysis | Pregnancy to birth | Health care funder | None | None | Cost-effectiveness |
| Ngeow (2015) [179] | Probabilistic cost-effectiveness analysis of cascade screening for familial hypercholesterolaemia using alternative diagnostic and identification strategies | Lifetime | Societal | 3.0% | 3.0% | Cost-utility and cost-effectiveness |
| Nherera (2011)[180] | Cost-effectiveness of carrier screening for cystic fibrosis in Australia | Lifetime | Health care funder | 3.5% | 3.5% | Cost-utility |

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| Norman (2012)[181] | BRCA mutation carrier detection: A model-based cost-effectiveness analysis comparing the traditional family history approach and the testing of all patients with breast cancer | Lifetime | Health care funder | 5.0% | 5.0% | Cost-effectiveness |
| Norum (2014)[182] | Cost effectiveness of newborn screening for cystic fibrosis: A simulation study | Lifetime | Societal | 3.0% | 3.0% | Cost-effectiveness |
| Nshimyumukiza (2014)[183] | Cell-free DNA-based non-invasive prenatal screening for common aneuploidies in a Canadian province: A cost-effectiveness analysis | 5 years | Health care funder | 3.0% | None | Cost-effectiveness |
| Nshimyumukiza (2018)[184] | Estimated cost-effectiveness of genetic testing in siblings of newborns with cancer susceptibility gene variants | Pregnancy to birth | Health care funder | None | None | Cost-effectiveness |
| O'Brien (2021)[185] | The role of noninvasive prenatal testing as a diagnostic versus a screening tool: A cost-effectiveness analysis | Lifetime | Health care funder | 3.0% | 3.0% | Cost-effectiveness |
| Ohno (2013)[186] | Economic analysis of prenatal screening strategies for Down syndrome in singleton pregnancies in Turkey | Lifetime | Societal | 3.0% | 3.0% | Cost-utility |
| Ökem (2017)[187] | An evaluation of the cost-effectiveness of comprehensive MTM integrated with point-of-care phenotypic and genetic testing for U.S. elderly patients after percutaneous coronary intervention | Pregnancy to birth | Health care funder + patient | None | None | Cost-effectiveness |
| Okere (2018)[188] | The price of performance: A cost and performance analysis of the implementation of cell-free fetal DNA testing for Down syndrome in Ontario | 21 years | Health care funder | 3.5% | 3.5% | Cost-utility |
| Okun 2014[189] | Cascade screening based on genetic testing is cost-effective: Evidence for the implementation of models of care for familial hypercholesterolemia | Pregnancy to birth | Health care funder | None | None | Cost-effectiveness |

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| O'Leary (2013)[190] | Prenatal screening for Down syndrome in Australia: Costs and benefits of current and novel screening strategies | Pregnancy to birth | Health care funder | None | None | Cost-effectiveness |
| Olgiati (2012)[191] | Should pharmacogenetics be incorporated in major depression treatment? Economic evaluation in high- and middle-income European countries | NR, Short horizon | Health care funder | None | None | Cost-utility |
| Panattoni (2012)[192] | The cost effectiveness of genetic testing for CYP2C19 variants to guide thienopyridine treatment in patients with acute coronary syndromes: A New Zealand evaluation | Lifetime | Health care funder | 3.0% | 3.0% | Cost-utility |
| Parthan (2013)[193] | Cost effectiveness of targeted high-dose atorvastatin therapy following genotype testing in patients with acute coronary syndrome | Lifetime | Health care funder | 3.0% | 3.0% | Cost-utility |
| Pastorino (2020)[194] | Cost-effectiveness analysis of genetic diagnostic strategies for Lynch syndrome in Italy | Lifetime | Health care funder | 3.0% | 3.0% | Cost-utility |
| Patel (2014)[195] | Cost-utility analysis of genotype-guided antiplatelet therapy in patients with moderate-to-high risk acute coronary syndrome and planned percutaneous coronary intervention | 15 months | Health care funder | 5.0% | 5.0% | Cost-utility |
| Patel (2018)[196] | Cost effectiveness of population based BRCA1 founder mutation testing in Sephardi Jewish women | Lifetime | Health care funder | 3.5% | 3.5% | Cost-utility |
| Pelczarska (2018)[197] | The cost-effectiveness of screening strategies for familial hypercholesterolaemia in Poland | Lifetime | Health care funder | 3.5% | 3.5% | Cost-utility and cost-effectiveness |
| Pereira (2019)[198] | Cost-utility analysis of genetic polymorphism universal screening in colorectal cancer prevention by detection of high-risk individuals | Lifetime | Societal | 3.0% | 3.0% | Cost-utility |

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| Perez (2011)[199] | Cost-effectiveness of genetic testing in family members of patients with long-QT syndrome | NR | Health care funder | 3.0% | 3.0% | Cost-utility |
| Pichereau (2010)[200] | Cost-effectiveness of UGT1A128 genotyping in preventing severe neutropenia following FOLFIRI therapy in colorectal cancer | NR, genotyping of patients -> second chemotherapy | Health care funder | None | None | Cost-effectiveness |
| Plumpton (2015)[201] | Cost-effectiveness of screening for HLA-A31:01 prior to initiation of carbamazepine in epilepsy | lifetime | Health care funder | 3.5% | 3.5% | Cost-utility and cost-effectiveness |
| Ramdzan (2021)[202] | Cost-effectiveness of colorectal cancer genetic testing | 10 years | Health care funder | 3.0% | 3.0% | Cost-utility and cost-effectiveness |
| Ramos (2018)[203] | Cost effectiveness of the cancer prevention program for carriers of the BRCA1/2 mutation | 40 years | Health care funder | 5.0% | 5.0% | Cost and consequence |
| Rens (2020)[204] | Cost-effectiveness of a pharmacogenomic test for stratified isoniazid dosing in treatment of active tuberculosis | lifetime | Health care funder | 3.0% | 3.0% | Cost-utility |
| Romanus (2015)[205] | Cost-effectiveness of multiplexed predictive biomarker screening in non-small-cell lung cancer | 2 years | Societal | 3.0% | 3.0% | Cost-utility and cost-effectiveness |
| Saito (2017)[206] | Cost-effectiveness analysis of the use of comprehensive molecular profiling before initiating monoclonal antibody therapy against metastatic colorectal cancer in Japan | 5 years | Health care funder | 2.0% | 2.0% | Cost-utility and cost-effectiveness |
| Saito (2019)[207] | Cost-effectiveness of BRCA1/2 mutation profiling to target olaparib use in patients with metastatic breast cancer | 5 years | Health care funder | 2.0% | 2.0% | Cost-utility |

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| Salikhanov (2021)[208] | Swiss cost-effectiveness analysis of universal screening for Lynch syndrome of patients with colorectal cancer followed by cascade genetic testing of relatives | Lifetime | Health care funder | 3.0% | 3.0% | Cost-utility |
| Sanford Kobayashi (2022)[209] | Cost efficacy of rapid whole genome sequencing in the pediatric intensive care unit | NR | Health care funder | None | None | Cost-utility and cost-effectiveness |
| Saokaew (2014)[210] | Cost-effectiveness analysis of HLA-B5801 testing in preventing allopurinol-induced SJS/TEN in Thai population | Lifetime | Societal | 3.0% | 3.0% | Cost-utility |
| Saramago (2018)[211] | High-throughput non-invasive prenatal testing for fetal rhesus D status in RhD-negative women not known to be sensitised to the RhD antigen: A systematic review and economic evaluation | 34 weeks | Health care funder | 3.5% | 3.5% | Cost-utility |
| Saramago (2018a)[212] | High-throughput, non-invasive prenatal testing for fetal rhesus D genotype to guide antenatal prophylaxis with anti-D immunoglobulin: A cost-effectiveness analysis | lifetime | Health care funder | 3.5% | 3.5% | Cost-utility |
| Schackman (2013)[213] | Cost-effectiveness analysis of UGT1A1 genetic testing to inform antiretroviral prescribing in HIV disease | lifetime | Health care funder | 3.0% | 3.0% | Cost-utility |
| Schluckebier (2020)[214] | Cost-effectiveness analysis comparing companion diagnostic tests for EGFR, ALK, and ROS1 versus next-generation sequencing (NGS) in advanced adenocarcinoma lung cancer patients | 5 years | Health care funder | 5.0% | 5.0% | Cost-effectiveness |
| Schofield (2019)[215] | Long-term economic impacts of exome sequencing for suspected monogenic disorders: Diagnosis, management, and reproductive outcomes | 20 years | Health care funder | 5.0% | 5.0% | Cost-utility |

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| Severin (2015)[216] | Economic evaluation of genetic screening for Lynch syndrome in Germany | Lifetime | Health care funder | 3.0% | 3.0% | Cost-effectiveness |
| Shang (2021)[217] | Introducing the non-invasive prenatal testing for detection of Down syndrome in China: A cost-effectiveness analysis | Pregnancy until birth | Health care funder | None | None | Cost-effectiveness |
| Shiffman (2012)[218] | Cost-effectiveness model of use of genetic testing as an aid in assessing the likely benefit of aspirin therapy for primary prevention of cardiovascular disease | 10 years | Health care funder | 3.5% | 3.5% | Cost-utility and cost-effectiveness |
| Shiroiwa (2010)[219] | Cost-effectiveness analysis of KRAS testing and cetuximab as last-line therapy for colorectal cancer | 2.5 years | Health care funder | 3.0% | 3.0% | Cost-utility and cost-effectiveness |
| Sie (2014)[220] | Fourfold increased detection of Lynch syndrome by raising age limit for tumour genetic testing from 50 to 70 years is cost-effective | Lifetime | Health care funder | 4.0% | 4.0% | Cost-effectiveness |
| Simoes Correa-Galendi (2021)[221] | Economic modelling of screen-and-treat strategies for Brazilian women at risk of hereditary breast and ovarian cancer | Lifetime | Health care funder | 5.0% | 5.0% | Cost-utility |
| Simons (2021)[222] | Early cost effectiveness of whole-genome sequencing as a clinical diagnostic test for patients with inoperable stage IIIB,C/IV non-squamous non-small-cell lung cancer | Lifetime | Societal | 4.0% | 1.5% | Cost-utility |
| Sluiter (2019)[223] | An economic model of the cost-utility of pre-emptive genetic testing to support pharmacotherapy in patients with major depression in primary care | 12 weeks | Societal | None | None | Cost-utility |

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| Snowsill (2014)[224] | A systematic review and economic evaluation of diagnostic strategies for Lynch syndrome | Lifetime | Health care funder | 3.5% | 3.5% | Cost-utility |
| Snowsill (2015)[225] | A model-based assessment of the cost-utility of strategies to identify Lynch syndrome in early-onset colorectal cancer patients | Lifetime | Health care funder | 3.5% | 3.5% | Cost-utility |
| Snowsill (2017)[226] | Molecular testing for Lynch syndrome in people with colorectal cancer: Systematic reviews and economic evaluation | NR, No time component | Health care funder | 3.5% | 3.5% | Cost-utility |
| Snowsill (2020)[227] | Cost-effectiveness of the Manchester approach to identifying Lynch syndrome in women with endometrial cancer | Lifetime (CUA), short term (CEA) | Health care funder | 3.5% | 3.5% | Cost-utility and cost-effectiveness |
| Somigliana (2019)[228] | Cost-effectiveness of preimplantation genetic testing for aneuploidies | ART treatment to birth | Health care funder | None | None | Cost-effectiveness |
| Song (2013)[229] | Clinical utility and cost of non-invasive prenatal testing with cfDNA analysis in high-risk women based on a US population | First 5 years of life | Societal | 3.0% | None | Cost-effectiveness |
| Stark (2017)[230] | Prospective comparison of the cost-effectiveness of clinical whole-exome sequencing with that of usual care overwhelmingly supports early use and reimbursement | referral until diagnosis, treatment period | Health care funder | None | None | Cost-effectiveness |
| Stark (2019)[231] | Does genomic sequencing early in the diagnostic trajectory make a difference? A follow-up study of clinical outcomes and cost-effectiveness | 18 months | Health care funder | None | None | Cost-utility and cost-effectiveness |
| Steuten (2019)[232] | Cost effectiveness of multigene panel sequencing for patients with advanced non-small-cell lung cancer | lifetime | Health care funder | 3.0% | 3.0% | Cost-effectiveness |

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| Su (2021)[233] | Cost-effectiveness of genomic test-directed olaparib for metastatic castration-resistant prostate cancer | Lifetime | Health care funder | 3.0% | 3.0% | Cost-utility |
| Sun (2019)[234] | A cost-effectiveness analysis of multigene testing for all patients with breast cancer | Lifetime | Societal | 3.5% | 3.5% | Cost-utility and cost-effectiveness |
| Sun (2022)[235] | Cost-effectiveness of genetic testing for all women diagnosed with breast cancer in China | Lifetime | Societal and health care funder | 3.0% | 3.0% | Cost-utility |
| Sutherland (2019)[236] | Economic evaluation of a novel genetic screening test for risk of venous thromboembolism compared with standard of care in women considering combined hormonal contraception in Switzerland | lifetime | Societal, health care funder +/- patient | 3.0% | 3.0% | Cost-utility |
| Szczepura (2011)[237] | A new fetal RHD genotyping test: Costs and benefits of mass testing to target antenatal anti-D prophylaxis in England and Wales | NR | Health care funder | None | None | Cost-effectiveness |
| Tan (2020)[238] | Utility of incorporating next-generation sequencing (NGS) in an Asian non-small cell lung cancer (NSCLC) population: Incremental yield of actionable alterations and cost-effectiveness analysis | <1 yr | Health care funder | None | None | Cost-effectiveness |
| Tanner (2020)[239] | Cost-effectiveness of combinatorial pharmacogenomic testing for depression from the Canadian public payer perspective | 5 years | Health care funder | 3.0% | 3.0% | Cost-utility |
| Teitelbaum (2015)[240] | Costs and benefits of non-invasive fetal RhD determination | Pregnancy to birth | Health care funder | None | None | Cost and consequence |

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| Teng (2020)[241] | Is HLA-B58:01 genotyping cost effective in guiding allopurinol use in gout patients with chronic kidney disease? | 1 year | Health care funder | 3.0% | 3.0% | Cost-utility |
| Tsai (2015)[242] | Cost-effectiveness analysis of carrier and prenatal genetic testing for X-linked hemophilia | Lifetime | Societal | None | None | Cost-effectiveness |
| Tsiplova (2017)[243] | A microcosting and cost-consequence analysis of clinical genomic testing strategies in autism spectrum disorder | 5 years | Health care funder | 3.0% | None | Cost-effectiveness |
| Tuffaha (2018)[244] | Cost-effectiveness analysis of germ-line BRCA testing in women with breast cancer and cascade testing in family members of mutation carriers | Lifetime | Health care funder | 5.0% | 5.0% | Cost-utility |
| Vallejo-Torres (2015)[245] | Cost-effectiveness analysis of a national newborn screening program for biotinidase deficiency | Lifetime | Health care funder | 3.0% | 3.0% | Cost-utility |
| Van der Ploeg (2015)[246] | Cost-effectiveness of newborn screening for cystic fibrosis determined with real-life data | Lifetime | Health care funder | 3.0% | 3.0% | Cost-effectiveness |
| Van Nguyen (2017)[247] | Incremental cost-effectiveness of algorithm-driven genetic testing versus no testing for maturity onset diabetes of the young (MODY) in Singapore | 30 years | Health care funder | 3.5% | 3.5% | Cost-utility |
| Vidavalur (2021)[248] | Economic evaluation of point of care universal newborn screening for glucose-6-phosphate dehydrogenase deficiency in United States | Lifetime | Health care funder | 3.0% | 3.0% | Cost-utility |

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| Vijayaraghavan (2012)[249] | Cost-effectiveness of KRAS testing in metastatic colorectal cancer patients in the United States and Germany | lifetime | Health care funder | None | None | Cost-effectiveness |
| Walker (2015)[250] | A cost-effectiveness analysis of first trimester non-invasive prenatal screening for fetal trisomies in the United States | Lifetime | Societal and funder | 3.0% | None | Cost-effectiveness |
| Walker (2015a)[251] | A cost-effectiveness analysis of cell free DNA as a replacement for serum screening for Down syndrome | Lifetime | Societal | None | None | Cost-effectiveness |
| Wanapirak (2019)[252] | Fetal Down syndrome screening models for developing countries; Part II: Cost-benefit analysis | Lifetime | Societal and funder | None | None | Cost-benefit |
| Wang (2012)[24] | Influence of patient preferences on the cost-effectiveness of screening for Lynch syndrome | Lifetime | Health care funder | 3.0% | 3.0% | Cost-utility |
| Wang (2012a)[253] | Predictive genetic testing of first degree relatives of mutation carriers is a cost-effective strategy in preventing hereditary nonpolyposis colorectal cancer in Singapore | Lifetime | Health care funder | 3.0% | 3.0% | Cost-effectiveness |
| Wei (2019)[254] | CYP2D6∗10 pharmacogenetic-guided SERM could be a cost-effective strategy in Chinese patients with hormone receptor-positive breast cancer | 30 years | Societal | 3.0% | 3.0% | Cost-utility |
| Wei (2020)[255] | Cost-effectiveness analysis of CYP2D610 pharmacogenetic testing to guide the adjuvant endocrine therapy for postmenopausal women with estrogen receptor positive early breast cancer in China | NR | Societal | 3.0% | 3.0% | Cost-utility |

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| Westwood (2014)[256] | KRAS mutation testing of tumours in adults with metastatic colorectal cancer: A systematic review and cost-effectiveness analysis | lifetime | Health care funder | 3.5% | 3.5% | Cost-utility |
| Westwood (2014a)[257] | Epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation testing in adults with locally advanced or metastatic non-small cell lung cancer: A systematic review and cost-effectiveness analysis | 6 years | Health care funder | 3.5% | 3.5% | Cost-utility and cost-effectiveness |
| Wong (2021)[258] | Cost effectiveness analysis of a polygenic risk tailored breast cancer screening programme in Singapore | 40 years | Health care funder | 3.0% | 3.0% | Cost-utility |
| Wordsworth (2010)[259] | DNA testing for hypertrophic cardiomyopathy: A cost-effectiveness model | Lifetime | Health care funder | 3.5% | 3.5% | Cost-effectiveness |
| Wu (2022)[25] | Genomic sequencing for the diagnosis of childhood mitochondrial disorders: A health economic evaluation | First consultation until 18 years old | Health care funder | 5.0% | 5.0% | Cost-benefit and cost-effectiveness |
| Wu (2018)[260] | Cost-effectiveness of osimertinib for EGFR mutation-positive non-small cell lung cancer after progression following first-line EGFR TKI therapy | 10 years | Health care funder | 3.0% | 5.0% | Cost-utility and cost-effectiveness |
| Xie (2020)[261] | Noninvasive prenatal testing for trisomies 21, 18, and 13, sex chromosome aneuploidies, and microdeletions in average-risk pregnancies: A cost-effectiveness analysis | Pregnancy to birth | Health care funder | None | None | Cost-effectiveness |
| Xu (2019)[29] | Cost-effectiveness analysis of non-invasive prenatal testing for Down syndrome in China | Pregnancy to birth | Societal | None | None | Cost-effectiveness |

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| Yuen (2018)[262] | Cost-effectiveness of genome and exome sequencing in children diagnosed with autism spectrum disorder | 2 years | Societal and funder | 3.0% | 3.0% | Cost-effectiveness |
| Yuliwulandari (2021)[263] | Cost-effectiveness analysis of genotyping for HLA-B15:02 in Indonesian patients with epilepsy using a generic model | Lifetime | Health care funder | 3.0% | 3.0% | Cost-utility |
| Zarca (2020)[264] | Cost-effectiveness analysis of pretreatment screening for NUDT15 defective alleles | 1 year | Health care funder | None | None | Cost-effectiveness |
| Zhang (2019)[265] | Cost-effectiveness of prenatal screening and diagnostic strategies for Down syndrome: A microsimulation modeling analysis | 18 years | Health care funder + patient | 3.0% | 3.0% | Cost-utility |
| Zhao (2022)[266] | Newborn screening for inherited metabolic diseases using tandem mass spectrometry in China: Outcome and cost-utility analysis | Lifetime | Societal | 5.0% | 5.0% | Cost and consequence |
| Zhu (2020)[267] | A model-based cost-effectiveness analysis of pharmacogenomic panel testing in cardiovascular disease management: Preemptive, reactive, or none? | lifetime | Health care funder | 3.0% | 3.0% | Cost-utility |
| Zou (2022)[268] | Diagnostic value and cost-effectiveness of next generation sequencing-based testing for treatment of patients with advanced/metastatic non-squamous non-small cell lung cancer in the US | Lifetime | Health care funder | 3.0% | 3.0% | Cost-utility and cost-effectiveness |

## Section E. Supplementary material references


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# Chapter 3.

# Impact of structural differences on the modelled cost-effectiveness of non-invasive prenatal testing

The comprehensive review in Chapter 2 found that non-invasive prenatal testing (NIPT) was an appropriate case study for exploring the challenges of economic modelling in genetic and genomic testing. Building on this review, this chapter presents a published systematic review of economic models of NIPT for the detection of chromosomal abnormalities (including Down syndrome), involving assessment of more information on model structure than was the case in the manuscript presented in Chapter 2. It set the stage for the construction of four demonstration models of NIPT with varying complexities based on the number of health states (three vs. five) and the modelling approach (decision tree vs. microsimulation) and populating them with consistent parameters. The article culminates in an analysis of the impact of different model structures on cost-effectiveness.

This chapter addresses key challenge 1, Model Structure, by advancing our understanding of economic modelling of NIPT, providing a recommendation for the most appropriate model structure in this context, and elucidating the impact of model structure on economic modelling outcomes and decision making more generally. It presents the core models that are explored in detail in the remainder of the thesis. The article was published as:

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# Impact of Structural Differences on the Modeled Cost-Effectiveness of Noninvasive Prenatal Testing

**Amber Salisbury, Alison Pearce, Kirsten Howard, and Sarah Norris**

**Background.** Noninvasive prenatal testing (NIPT) was developed to improve the accuracy of prenatal screening to detect chromosomal abnormalities. Published economic analyses have yielded different incremental cost-effective ratios (ICERs), leading to conclusions of NIPT being dominant, cost-effective, and cost-ineffective. These analyses have used different model structures, and the extent to which these structural variations have contributed to differences in ICERs is unclear. **Aim.** To assess the impact of different model structures on the cost-effectiveness of NIPT for the detection of trisomy 21 (T21; Down syndrome). **Methods.** A systematic review identified economic models comparing NIPT to conventional screening. The key variations in identified model structures were the number of health states and modeling approach. New models with different structures were developed in TreeAge and populated with consistent parameters to enable a comparison of the impact of selected structural variations on results. **Results.** The review identified 34 economic models. Based on these findings, demonstration models were developed: 1) a decision tree with 3 health states, 2) a decision tree with 5 health states, 3) a microsimulation with 3 health states, and 4) a microsimulation with 5 health states. The base-case ICER from each model was 1) USD$34,474 (2023)/quality-adjusted life-year (QALY), 2) USD$14,990 (2023)/QALY, (3) USD$54,983 (2023)/QALY, and (4) NIPT was dominated. **Conclusion.** Model-structuring choices can have a large impact on the ICER and conclusions regarding cost-effectiveness, which may inadvertently affect policy decisions to support or not support funding for NIPT. The use of reference models could improve international consistency in health policy decision making for prenatal screening.

**Corresponding Author**
Amber Salisbury, Menzies Centre for Health Policy and Economics, Sydney School of Public Health, University of Sydney, Sydney, NSW, Australia; The Daffodil Centre, University of Sydney, a joint venture with Cancer Council NSW, Sydney, Australia (amber.salisbury@sydney.edu.au).

**Highlights**

- NIPT is a clinical area in which a variety of modeling approaches have been published, with wide variation in reported cost-effectiveness.
- This study shows that when broader contextual factors are held constant, varying the model structure yields results that range from NIPT being less effective and more expensive than conventional screening (i.e., NIPT was dominated) through to NIPT being more effective and more expensive than conventional screening with an ICER of USD$54,983 (2023)/QALY.
- Model-structuring choices may inadvertently affect policy decisions to support or not support funding of NIPT. Reference models could improve international consistency in health policy decision making for prenatal screening.

**Keywords**
noninvasive prenatal testing, NIPT, prenatal screening, health economic modeling, economic evaluation, structural uncertainties, decision tree, microsimulation, cost-effectiveness analyses, cost-utility analyses

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Health technology assessment (HTA) agencies provide advice on the funding of health technologies in many countries[1] and typically rely on economic models to evaluate the comparative costs and benefits of these technologies. The stages of building a model are 1) selecting the analytical methods, 2) creating the structure, and 3) populating the model.[2] As there is seldom complete information regarding the technology and how it will be used in clinical practice, different choices can be made at each stage of model development, which can generate significant uncertainty for decision makers.

The 3 main types of uncertainty in models are methodological, parameter, and structural.[3] Methodological uncertainty includes differences in the analytic methods or the approach taken to build the model: the perspective chosen, the discount procedure/rate applied, or the way health gains are valued. Parameter uncertainty deals with the precision of the numerical value of inputs and is related to data quality. Structural uncertainty describes assumptions and simplifications within the model and the relationship between input parameters. The definition of structural uncertainty is often interpreted differently, resulting in apparent overlap between the different types of uncertainty.

In this article, we adopt an operational interpretation of structural uncertainty, which encompasses aspects of uncertainty that are often overlooked. Different choices can be made at each step of the structuring process, each leading to uncertainties. The first step is conceptual modeling, which involves selecting clinically/economically important health states and relevant patient attributes to include within the model. The second step is to make structural choices, which determine how model inputs are interrelated and estimated, such as the relationship between time and risk of an event, or the survival model used. The last step is the choice of modeling technique, for example, choosing between a decision tree or a Markov model. This choice reflects the complexity of the model and is influenced by decisions made in the previous steps. In considering the difference between structural and parameter

Menzies Centre for Health Policy and Economics, Sydney School of Public Health, University of Sydney, Sydney, NSW, Australia (AS, KH, SN); The Daffodil Centre, University of Sydney, a joint venture with Cancer Council NSW, Sydney, Australia (AS, AP); Sydney School of Public Health, University of Sydney, Sydney, NSW, Australia (AP).
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uncertainty, we have taken the view that selection of patient attributes (including sociodemographic attributes such as age or gender, clinical attributes such as comorbidities or previous diseases, and lifestyle and behavioral attributes such as smoking or alcohol consumption) for inclusion within the model represents structural uncertainty, whereas the values assigned for each of these attributes represents parameter uncertainty. The approaches for handling parameter and methodological uncertainty are well established in the literature, while approaches for handling structural uncertainty are not.[4,5]

Differences in model structure are known to affect model predictions. In economic evaluations of lapatinib for breast cancer, different Markov model structures (alternative health states and transitions) resulted in a wide range of incremental cost-effective ratios (ICERs), differing by more than USD$250,000 (2016)/quality-adjusted life-year (QALY).[6] Similarly, when evaluating adjuvant endocrine breast cancer treatment, changing the number of health states resulted in a 21.7% change in life-years gained and a 16.8% change in the ICER.[7] A more recent study explored the impact of different modeling approaches on modeled results within diabetes and found microsimulation models generated a mean of 3.41 life-years more than cohort simulation models did.[8] These studies demonstrate model structure has the potential to affect results and conclusions regarding cost-effectiveness, which may in turn affect funding decisions.

Noninvasive prenatal testing (NIPT) is a clinical area in which a variety of modeling approaches have been published, with wide variation in the modeled cost-effectiveness ratios. NIPT uses fetal DNA circulating in maternal plasma to detect 3 common trisomies (T21, Down syndrome; T18, Edwards syndrome; and T13, Patau syndrome) in the fetus.[9] NIPT can be offered as a first-line test, replacing combined first-trimester screening (cFTS; ultrasound measurement of fetal nuchal translucency and maternal serum biochemical marker evaluation of β–human chorionic gonadotropin and pregnancy-associated plasma protein A) or as a second-line test after cFTS. It is claimed that NIPT offers a higher detection rate and lower false-positive rate compared with conventional screening methods.[10] A previous systematic review identified 16 economic evaluations of NIPT with differing cost-effectiveness results.[11] Fourteen studies assessed NIPT as a first-line test, and of these, 9 studies found NIPT was more expensive and more effective, 4 studies found NIPT was dominant (i.e., more effective and less expensive), and 1 found it was dominated (i.e., less effective and more expensive). Fifteen studies evaluated NIPT as a second-line test, and of these, 8 studies found NIPT was more expensive and more effective, 3 studies found NIPT was dominant, 1 study found NIPT was dominated, and 3 studies found NIPT was less effective and less expensive. The review identified variations in the time horizon, health outcomes, and contextual factors (such as year of analysis and currency) across the included studies, which the authors suggested were likely to have caused the different results. Other reviews of NIPT economic evaluations have assessed the cost-effectiveness of NIPT[11–13] and the extent to which evaluations have accounted for the resourcing needed to provide counseling alongside testing.[14] To our knowledge, no published economic evaluation or review has explored the impact of different structural choices on the modeled cost-effectiveness of NIPT and, by extension, the extent to which such choices represent a source of uncertainty that has not been accounted for by decision makers.

## Methods

*Research Aims*

1. To describe differences in model structure for economic evaluations of NIPT for chromosomal abnormalities
2. To compare the impact of different model structures on modeled results

The analysis was performed in the following stages:

A. Systematic review of the literature to describe the structure of published economic models of NIPT
B. Development of new models evaluating NIPT for T21 with alternative structures, populated with parameters taken from the same sources (identified via supplementary targeted literature searches)
C. Comparison of modeled results from alternative model structures

*Stage A: Review of NIPT Model Structures*

*Information sources.* A broad systematic review of economic evaluations of genetic and genomic tests was conducted as background research for a number of studies, including the current study. For the broader review, systematic searches were conducted in 4 databases: EMBASE, Medline, SCOPUS, and EconLit. The systematic search strategy for the published literature was based on 2 concepts: 1) genetic/genomic testing (including specific search terms for NIPT) and 2) economic evaluations. The search span was January 1, 2010, to June

15, 2022. Search terms are presented in the Supplementary Materials (Table S1). An additional search of HTA agency Web sites was performed in January 2023, using search terms for prenatal testing. Bibliographic review of included reviews and HTA reports was undertaken to capture additional studies that had not been identified in the electronic literature search.

*Eligibility criteria*. Model-based economic evaluations of NIPT that considered the costs and consequences of NIPT were eligible for inclusion, namely, cost-effectiveness (CEA), cost-utility (CUA), cost-benefit, cost-consequence, and threshold analyses. Trial-based studies, costing studies, budget impact analyses, nonhuman, and non-English studies were excluded.

*Quality assessment*. Quality assessment was performed using the Drummond checklist.[15] A rating scale was used to attribute a possible score of 1 to each item on the checklist.[16] The aggregate results provide an assessment of quality: poor (1–3 points), average (4–7 points), and good (8–10 points). The authors preagreed that studies scoring between 1 and 3 points would be excluded from the final analysis.

*Data extraction*. Study characteristics were extracted by a single reviewer (A.S.) and checked by a second reviewer (S.N.). The data extraction template was based on the Methods section of the CHEERS checklist[15] and included the base-case results of each study. Study characteristics included country, study type, perspective, time horizon, clinical condition, discount rates, primary outcome measure(s), and type of sensitivity analysis. For each included study, a single reviewer (A.S.) documented elements of model structure within an Excel sheet and recorded whether study authors justified their chosen modeling approach, tested the impact of different modeling approaches within a sensitivity analysis, and/or provided a discussion of the potential impacts of their choices regarding model structure. For identified CUAs, the value of utility weights for a given health state, the source of each utility weight, and the method used to derive utility weights were also extracted.

*Comparison of results from included studies*. The base-case ICERs of included studies assessing NIPT as a second-line test against conventional screening were compared using a cost-effectiveness plane. We focused on second-line testing as a previous review[11] identified a wider range of cost-effectiveness outcomes when considering NIPT as a second-line test as opposed to a first-line test. In addition, second-line NIPT has been considered for government funding in Australia[16] and is therefore particularly relevant to our local policy context. It should be noted that "conventional screening" differed among the included studies, and where multiple comparator screening strategies were evaluated, the results for combined FTS against second-line NIPT were presented. To facilitate direct comparison of the published ICERs, reported incremental costs were converted to USD (2023) using Organisation for Economic Co-operation and Development (OECD) purchasing power parity[17] and inflators from the total health price index.[18]

### *Stage B: Building Alternative Model Structures*

Our model-structuring process (model conceptualization, structural choices, and choice of modeling technique) was informed by the systematic review in stage A and consultation with experts including obstetricians (A.S., L.B.) and health economics/policy experts (K.H., A.P., S.N.). Additional advice on clinical practice was sought from 2 obstetricians, a genetic counselor, a midwife, and an individual with lived experience.

The expert consultation was crucial for determining a model structure that maximized the fit to pathology and practice by incorporating all relevant health states and patient attributes, given the available data. The literature review identified common NIPT model structures, enabling our selection of structures for comparison.

Four demonstration models with different structures were developed within TreeAge, comparing 3 versus 5 health states, and a decision tree approach versus microsimulation. Each of these was considered an appropriate model structure for our research purposes given the available evidence, expert opinion, and policy context (described in the "Results" section).

We defined the intervention as second-line NIPT. cFTS results were classified as high (risk score of >1:10), intermediate (risk score of >1:300), or low risk. It was assumed that women with a high risk result are offered invasive diagnostic testing, women with an intermediate risk result are offered NIPT, and women with a low risk result are not offered further testing. Women with a positive NIPT result are subsequently offered an invasive test. We have defined the comparator as conventional screening, in which women with a cFTS test risk of >1:300 are offered invasive diagnostic testing.

For each model structure, the population, comparator, time horizon, year of analysis, currency, and other core components were held constant to enable a comparison of

**Table 1** Core Components of Models Evaluating NIPT against cFTS

| Component | | Justification |
|---|---|---|
| Population | All singleton pregnancies regardless of trisomy risk | Simplification as different data are required for multiple pregnancies and these data are less reliable[19] |
| Setting | Australia | Australian context |
| Timing | All pregnant women enter at first trimester only | Simplification |
| Intervention | cFTS followed by NIPT in cFTS intermediate-risk pregnancies and invasive testing in cFTS high-risk pregnancies | Second-line testing is the most likely option to be funded in Australia |
| Comparator | cFTS with no NIPT and invasive testing in intermediate- or high-risk pregnancies | Current publicly funded testing in Australia |
| cFTS intermediate-risk cutoff | cFTS trisomy risk score of >1:300 | Based on clinical advice and local hospital guidelines[20] |
| cFTS high-risk cutoff | cFTS trisomy risk score of >1:10 | Based on clinical advice, this value ranges from 1/10 to 1/100; 1/10 is the conservative approach |
| Perspective | Health care funder | Local HTA guidelines[4] as we are interested in how modeling informs decision making |
| Types of aneuploidies | T21 | Simplification; T21 is being used as the case-study, but there will be implications for other uses of NIPT |
| Time horizon | Pregnancy duration | Simplification |
| Discount rate | None | Time horizon is less than 1 y |
| Currency | AUD and USD | AUD is presented as the model is set within the Australian context; costs are converted to USD to enable comparisons with other studies |
| Year of analysis | 2023 | Present context |

AUD, Australian dollars; cFTS, combined first-trimester screening; HTA, health technology assessment; NIPT, noninvasive prenatal testing; USD, US dollars.

the extent to which structural variations affected the modeled results. Nonetheless, the core components of each model were based on the clinical context in Australia and advice provided by 2 local obstetricians. The core components selected for the demonstration models, with justifications for these choices, are shown in Table 1.

Each model structure was populated with consistent parameters for costs, clinical inputs, utility weights, and transition probabilities. Clinical parameters were obtained from a large, randomized control trial,[10] and costs were obtained from the Australian Medical Benefits Schedule (see Supplementary Materials, Tables S5 and S6). A comprehensive supplementary literature review was conducted to identify appropriate utility weights. Based on this review, we used the utilities presented by Kuppermann et al.[21] (Table 2). Details can be found within the Supplementary Material (section C).

**Table 2** Utility Weights Used within Each Model

| Health State | Utility Weight | Source |
|---|---|---|
| T21 birth | 0.655 | Kuppermann 2016[21] |
| Unaffected birth | 1 | Assumption |
| Termination | 0.8 | Kuppermann 2016[21] |
| Procedure-related loss | 0.744 | Kuppermann 2016[21] |
| Spontaneous loss | 0.744 | Kuppermann 2016[21] |

All costs were converted to USD (2023) using the OECD purchasing power parity[21] (1 AUD 2023 = 0.705 USD 2023).

Key assumptions made in each model are as follows:

- Patients receive an initial GP appointment to discuss genetic testing options.

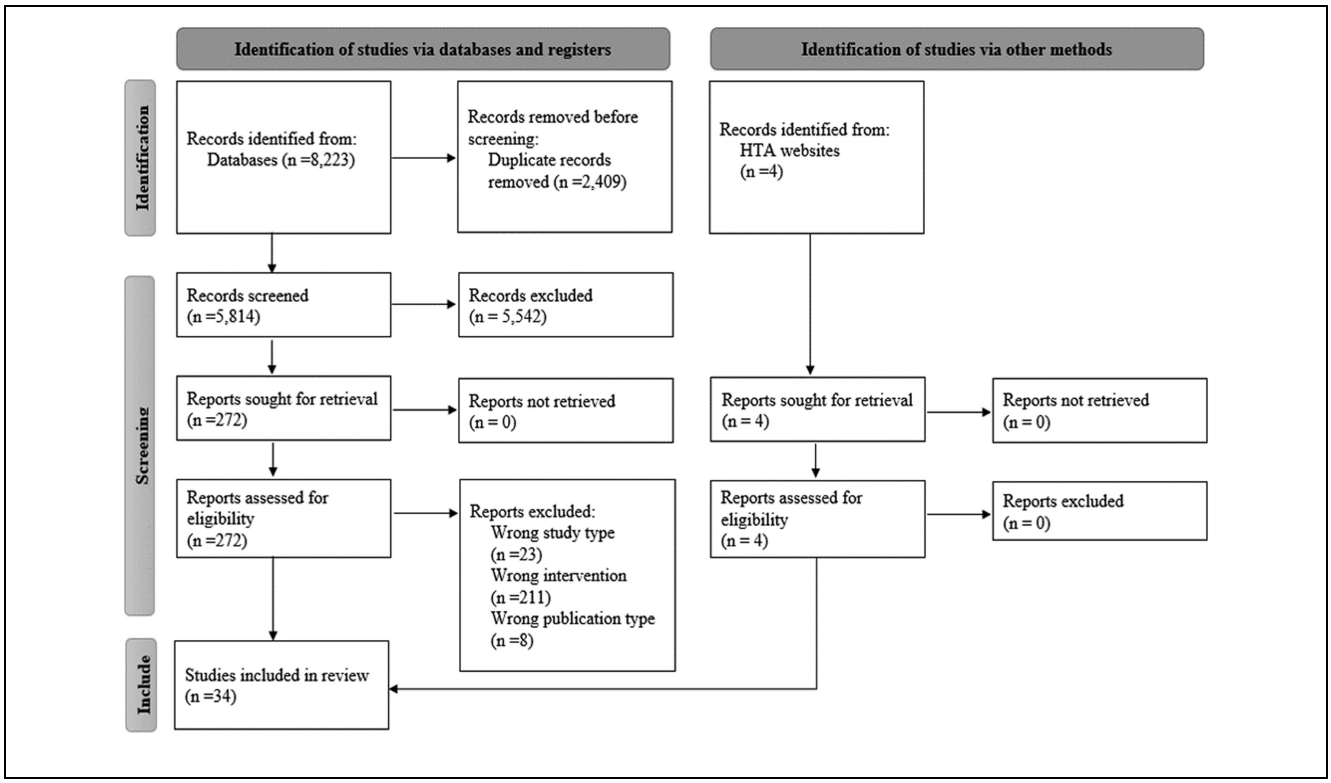


**Figure 1** PRISMA flow diagram.

- Patients with a positive result from screening have an appointment with their obstetrician, which includes genetic counseling.
- Patients who undergo invasive testing are provided with genetic counseling after testing, from the obstetrician.
- Patients with inconclusive NIPT results go directly to invasive testing.
- Invasive testing is 100% sensitive and specific.

Internal validation involved ensuring models maintained logical coherence when adjusting costs and utilities while also verifying that 1-way sensitivity analyses and scenario analyses yielded expected outcomes. External validation involved comparing the results of our models to the Australian models identified within the main review.

*Stage C: Comparison of ICERs from Different Model Structures*

For each model, we present the following results:

- the incremental cost/T21 detected,
- the incremental cost/procedure-related loss (PRL) avoided, and
- the incremental cost/QALY.

The results of each model are compared by examining the overall outcome of the model (i.e., NIPT dominant, NIPT dominated, NIPT more expensive and more effective, NIPT less expensive and less effective). One-way sensitivity analyses were performed on the following parameters using plausible extreme values: uptake rates of cFTS, NIPT, and invasive testing (after an intermediate-risk cFTS result, after a high-risk cFTS result, and after a positive-risk NIPT result) and cFTS and NIPT sensitivity and specificity. Distributions for the following parameters were included in the probabilistic analysis: spontaneous loss, NIPT and cFTS sensitivity and specificity, rates of pregnancy termination, and uptake rates of cFTS, NIPT, and invasive testing (after an intermediate-risk cFTS result, after a high-risk cFTS result, and after a positive-risk NIPT result).

The funding source had no role in the study.

## Results

*Stage A: Review of NIPT Model Structures*

The database search yielded 8,223 records published between January 1, 2010, and June 15, 2022 (Figure 1). After removing duplicates, 5,814 records were included

**Table 3** Basic Study Characteristics of Economic Models Comparing NIPT to Conventional Screening

| Study Characteristic ($N$ = 34) | Response | |
|---|---|---|
| | *n* | % |
| Study type | | |
| CEA | 23 | 68 |
| Cost and consequence | 4 | 12 |
| CUA | 3 | 9 |
| Threshold analysis | 3 | 9 |
| CBA | 1 | 3 |
| Perspective | | |
| Health care funder | 20 | 59 |
| Health care funder + patient | 8 | 24 |
| Societal | 4 | 12 |
| Societal and health care funder | 2 | 6 |
| Time horizon | | |
| Pregnancy until birth | 26 | 76 |
| 5 y | 1 | 3 |
| 18 y | 1 | 3 |
| Lifetime | 6 | 18 |
| Condition | | |
| T21 | 23 | 68 |
| T21, T18, and T13 | 8 | 24 |
| T21, T18, T13, and monosomy X | 2 | 6 |
| T21, T18, T13, sex chromosomes, and microdeletions | 1 | 3 |
| Uptake included? | | |
| Yes, with evidence | 23 | 68 |
| Yes, without evidence | 6 | 18 |
| No | 5 | 15 |

CBA, cost-benefit analysis; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; NIPT, noninvasive prenatal testing; T13, trisomy 13; T18, trisomy 18; T21, trisomy 21.

in the title/abstract screen, and 272 articles were obtained for full-text review. Based on full-text review, 30 studies met the inclusion criteria for this study, and 4 additional HTAs of NIPT were identified through HTA Web sites. Ten studies were scored as average quality, and 24 were scored as good quality. No studies were scored as poor quality, and thus all studies were included in this analysis. The quality assessment can be found in the Supplementary Materials (section D).

*Study characteristics*. Thirty-four studies were included, with studies conducted in the United States ($n$ = 10, 29%), Canada ($n$ = 7, 21%), Belgium ($n$ = 4, 12%), China ($n$ = 4, 12%), and other countries ($n$ = 9, 26%). Most studies conducted a CEA from a health care funder perspective, over the duration of pregnancy, and focused on T21 (Table 3). More than 60% of studies included uptake rates; however, these rates were mostly based on conventional screening evidence. See Supplementary Materials (Table S10) for more details.

*Structural elements*. The structural elements identified from the included studies are shown in Table 4. The number of health states included within the models ranged from 3 to 7, with 5 being the most common (53% of models). The 3 most common health states were live birth (unaffected), live birth (T21), and procedure-related loss (PRL), followed by "spontaneous loss" and "termination." The modeling approaches included decision trees ($n$ = 22, 65%), Markov models ($n$ = 7, 21%), and microsimulations ($n$ = 5, 15%). Four studies justified their modeling approach, and 2 studies included a discussion of their modeling approach. No study tested the impact of their approach on their modeled results.

*Results of included studies*. A comparison of the results of second-line NIPT against conventional screening is presented in Figure 2 ($n$ = 23). Six studies found NIPT was dominated (lower right-hand quadrant), 1 study found NIPT was dominant (upper left-hand quadrant), 8 studies found NIPT was less expensive and less effective (lower left-hand quadrant), and 8 studies found NIPT was more expensive and more effective (upper right-hand quadrant) (Figure 2a). There were large variations in the ICERs within the upper right-hand quadrant (Figure 2b).

*Cost-utility analyses*. Three CUAs were identified.[33,48,52] All studies used utility weights from the perspective of the mother and were derived from time-tradeoff studies.[53] The utilities for each health state and sources can be found within the Supplementary Materials (Table S11).

### *Stage B: Building Alternative Model Structures*

*Model conceptualization*. Based on the research question and expert consultation, the following patient attributes were considered relevant for inclusion:

- Impact of maternal age on the risk of Down syndrome
- Impact of maternal age on the risk of spontaneous loss

The following health states/events were considered relevant for inclusion:

**Table 4** Structural Elements of Identified Economic Models[a]

| | | Health State | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study ID** | **No. of Health States** | **Live Birth (Unaffected)** | **T21 Birth** | **Live Birth (Other)[b]** | **PRL** | **SPL** | **Termination[c]** | **Still Birth[c,d]** | **Pregnancy Loss and Child 2 ye Later** | **Pregnancy Loss and No Future Pregnancy** | **Uptake Considered[e]** | **Approach[f]** |
| Ayres 2015[22] | 3 | × | × | | × | | | | | | Y | Decision tree |
| Crimmins 2017[23] | 3 | × | × | | × | | | | | | N | Decision tree |
| Cuckle 2013[24] | 3 | × | × | | × | | | | | | Y | Decision tree |
| IHE 2014[25,26] | 3 | × | × | | × | | | | | | N | Decision tree |
| Maxwell 2017[27] | 3 | × | × | | × | | | | | | Y | Decision tree |
| Ökem 2017[28] | 3 | × | × | | × | | | | | | Y | Decision tree |
| Okun 2014[26] | 3 | × | × | | × | | | | | | Y* | Decision tree |
| O'Leary 2013[29] | 3 | × | × | | × | | | | | | Y* | Decision tree |
| Colosi 2017[30] | 4 | × | × | × | × | | | | | | N | Decision tree |
| Huang 2020[31] | 4 | × | × | | × | × | | | | | Y | Decision tree |
| Nshimyumukiza 2018[32] | 4 | × | × | | × | × | | | | | Y* | Decision tree |
| Anh 2021[33] | 5 | × | × | | × | × | × | | | | N | Decision tree |
| Bayón 2019[34] | 5 | × | × | | × | × | × | | | | Y* | Decision tree |
| Beulen 2014[35] | 5 | × | × | | × | | × | × | | | Y* | Decision tree |
| Kostenko 2019[36] | 5 | × | × | × | × | | | | | | Y* | **Decision tree** |
| Morris 2014[37] | 5 | × | × | | × | × | × | | | | Y* | Decision tree |
| MSAC 2019[16] | 5 | × | × | | × | × | × | | | | Y* | Decision tree |
| Shang 2021[38] | 5 | × | × | | × | × | × | | | | Y* | Decision tree |
| Wanapirak 2019[39] | 5 | × | × | | × | × | × | | | | Y* | Decision tree |
| Xu 2019[40] | 5 | × | × | | × | × | × | | | | Y* | **Decision tree** |
| Fairbrother 2016[41] | 6 | × | × | × | × | × | × | | | | Y* | Decision tree |
| Benn 2015[42] | 7 | × | × | × | × | × | × | | | | Y* | Decision tree |
| Garfield 2012[43] | 4 | × | × | × | × | | | | | | Y* | Markov |
| Gyselaers 2015[44] | 5 | × | × | | × | × | × | | | | Y* | Markov |
| KCE 2014[13] | 5 | × | × | | × | × | × | | | | Y* | Markov |
| Neyt 2014[45] | 5 | × | × | | × | × | × | | | | Y* | Markov |
| Hopkins 2020[46] | 6 | × | × | | × | × | × | | | | Y | Markov |
| Song 2013[47] | 6 | × | × | | | | × | × | | | Y* | Markov |
| Kaimal 2015[48] | 7 | × | × | × | | | | | × | × | N | Markov |
| HQO 2019[12] | 5 | × | × | | × | × | × | | | | Y* | Microsim |
| Walker 2015[49] | 5 | × | × | | × | × | × | | | | Y* | Microsim |
| Walker 2015[50] | 5 | × | × | | × | × | × | | | | Y* | Microsim |
| Xie 2020[51] | 7 | × | × | × | × | × | × | | | | Y* | **Microsim** |
| Zhang 2019[52] | 7 | × | × | | × | × | × | | × | × | Y* | **Microsim** |

Microsim; microsimulation, N; no, PRL; procedure-related loss, SPL; spontaneous pregnancy loss, Y; yes.

[a]Studies have been ordered by number of health states and then by modeling approach (decision tree, Markov model, microsimulation). This ordering attempts to reflect increasing model complexity. Gray highlighting with a cross indicates the health state has been included within the identified model.

[b]"Other" refers to the following conditions: microdeletions, sex chromosomes, and/or variants of unknown significance.

[c]Health states within this category are either labeled affected and/or not affected or the health state is unspecified. This column combines 3 different health states.

[d]Both spontaneous loss and stillbirth describe pregnancy loss, but they differ according to when the loss occurs (before and after 20 wk).

[e]"Y*" indicates uptake has been considered with evidence, "Y" indicates uptake has been considered without evidence, and "N" means uptake has not been considered.

[f]Studies that provided justification for their modeling approach and/or included potential impacts of the structure within the discussion are marked in bold (e.g., **Microsim** or **Decision tree)**.

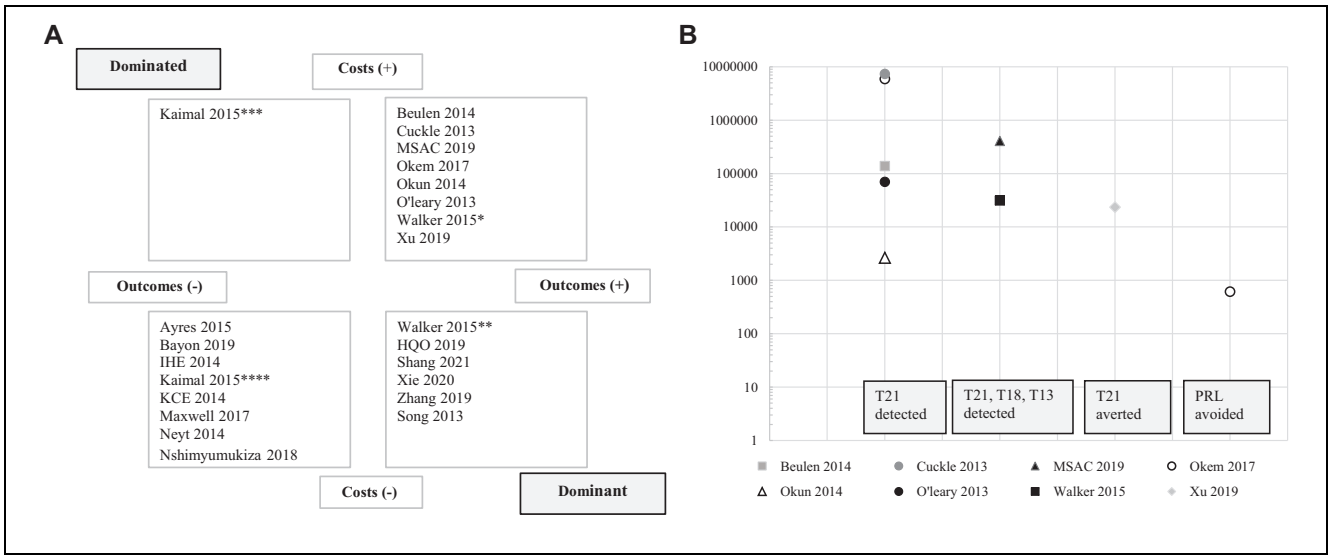


**Figure 2** (a) Cost-effectiveness plane for studies evaluating second-line NIPT against conventional screening. Incremental cost-effectiveness ratios for 4 different outcomes are presented: T21 detected; T21, T18, and T13 detected; T21 averted and PRL avoided. (b) Detailed view of the upper right-hand quadrant of the cost-effectiveness plane in Figure 2a. Each outcome is presented on a separate horizontal axis, and results are displayed using a log scale in 2023 USD.
NIPT, noninvasive prenatal testing; PRL, procedure-related loss; T, trisomy.
*Payer perspective.
**Government and societal perspective.
***Twenty- and 30-year-olds.
****Forty-year-olds.

- Final health states: live birth (T21), live birth (unaffected), termination, spontaneous loss, procedure-related loss
- Intermediate events: the anxiety and wait times associated with receiving a false-positive or inconclusive result

The systematic review found a large proportion of published models did not include termination and/or spontaneous loss. We built models to compare the impact of including all health states considered to be clinically relevant and a simplified model that does not include termination or spontaneous loss. Due to our decision to hold the time horizon constant across the models being explored, health states beyond 1 y (e.g., giving birth to a child 2 y later or no future pregnancy) were not included in our models.

A large number of the included published models did not include risks based on maternal age. We built models to compare the impact of including or excluding these risks. Due to a lack of available data, intermediate outcomes were not included within the published models or within our models.

*Structural choices.* Due to the short-term nature of our model (as decided in the methodological stage), extrapolation was not used, nor was survival analysis. There are no time dependencies within the model.

*Modeling techniques.* The choice of modeling technique stems from the model conceptualization. The least complicated but most feasible technique should be chosen.[54] Microsimulations are best used for complex models with large variability in the cohorts.[55] Consequently, we used a microsimulation approach to build the models that incorporate risks based on maternal age. When these risks were not incorporated, we used a decision tree, as there was no longer a need to use a microsimulation. An alternative approach to capturing different risks based on maternal age could be through subgroup analysis or by creating subtrees for different ages within a decision tree.

Within the systematic review, decision trees, Markov models, and microsimulations were identified. Markov models are best used for long-term chronic diseases, which incorporate time dependencies.[55] The identified Markov models did not incorporate any time

**Table 5** Alternative Model Structures to Compare Second-Line NIPT against cFTS

| Model ID | Modeling Approach | No. of Health States | Included Health States |
|---|---|---|---|
| Model D3 | Decision tree | 3 | Live birth (unaffected), live birth (T21), PRL |
| Model D5 | Decision tree | 5 | Live birth (unaffected), live birth (T21), PRL, spontaneous loss, termination |
| Model M3 | Microsimulation | 3 | Live birth (unaffected), live birth (T21), PRL |
| Model M5 | Microsimulation | 5 | Live birth (unaffected), live birth (T21), PRL, spontaneous loss, termination |

cFTS, combined first-trimester screening; NIPT, noninvasive prenatal testing; PRL, procedure-related loss.

dependencies and were not fundamentally different from the identified decisions trees. As we were not incorporating any time dependencies, a Markov model was not built.

*Overview of demonstration models*. Four alternative structures were created (Table 5), which differed by number of health states (3 or 5) and modeling approach (decision tree or microsimulation, reflecting the difference in incorporating risks based on maternal age). Diagrams of the model structures can be found in the Supplementary Materials (section H).

*Stage C: Comparison of Results*

The ICERs varied among the 4 models for each of the 3 outcomes evaluated (T21 detected, PRL avoided, and QALY). These results are presented in Table 6.

*Sensitivity analysis*. One-way and probabilistic sensitivity analyses are shown in the Supplementary Materials (Tables S12, S13, and S14). Uptake of NIPT and invasive testing were found to have the greatest impact on results. Uptake of cFTS was found to have minimal impact on results.

## Discussion

This study identified a large number of economic evaluations of NIPT with different model structures and cost-effectiveness results. By developing new models that hold model inputs constant but vary key structural components of number of health states (3 v. 5) and modeling approach (decision tree v. microsimulation), we demonstrate that variations in model structure alone can have large effects on cost-effectiveness results. For example, with a CUA, the ICERs ranged from NIPT being dominated (model M5), to being cost-effective (at the commonly referenced threshold of USD$50,000/QALY,[56] model D3 and D5) to being not cost-effective at more than USD$50,000/QALY (model M3). These findings demonstrate that model structure in this context represents a significant, previously unrecognized, source of uncertainty for decision makers who rely on model findings.

The systematic review identified 34 economic models comparing NIPT against conventional screening methods. Twelve additional studies were identified compared with recently conducted reviews,[11,12] highlighting the large volume of research in this area. Most studies conducted CEAs from the health care funder perspective and used a short time horizon. Although guidelines recommend conducting a CUA where possible,[4] most studies justified a CEA due to the paucity of published studies assessing utilities, particularly in the context of intermediate outcomes (such as the psychological impact of a false positive). In addition, QALYs have limitations in adequately capturing the benefits associated with new life,[57] and ethical concerns arise when valuing the life of a child with Down syndrome.[58]

Based on the included CUAs,[7,9,10] the main source of utility weights was a US time-tradeoff study. Although that study attempted to capture the impact of intermediate outcomes, only minor decrements in utility were found, and these findings do not align with the broader qualitative literature.[12,16] The authors of the time-tradeoff study hypothesize that the lack of impact is likely due to the methodology used, with participants focusing on final outcomes and overdiscounting intermediate outcomes. To adequately capture intermediate outcomes, it may be necessary to consider alternative valuation methods, such as discrete choice experiments.[14]

Our systematic review expands on previous reviews by extracting additional information on health states. A range of health states were identified, with the most common health states being live birth (T21), live birth (unaffected), and procedure-related loss, followed by termination and spontaneous loss health states, although they were not included in more than 40% of identified models. This study created demonstration models to

**Table 6** Results from Different Model Structures Evaluating cFTS versus NIPT from Pregnancy until Birth

| Model ID | Screening Strategy | Cost, USD 2023 (AUD 2023) | Incremental Cost, USD 2023 (AUD 2023) | Effect | Incremental Effect | ICER, USD 2023 (AUD 2023) | Outcome |
|---|---|---|---|---|---|---|---|
| Effect: T21 detected | | | | | | | |
| Model D3 | cFTS | 100.62 (142.81) | | 0.001578 | | | NIPT is more expensive and more effective |
| | NIPT | 101.43 (143.95) | 0.80 (1.14) | 0.001590 | 0.000012 | 66,936 (93,141) | |
| Model D5 | cFTS | 173.98 (246.92) | | 0.001578 | | | NIPT is more expensive and more effective |
| | NIPT | 174.82 (248.11) | 0.84 (1.19) | 0.001590 | 0.000012 | 69,872 (96,873) | |
| Model M3 | cFTS | 126.02 (178.85) | | 0.001613 | | | NIPT is dominated (more expensive and less effective) |
| | NIPT | 126.97 (180.20) | 0.95 (1.39) | 0.001603 | −0.000010 | −95,120 (−139,000) | |
| Model M5 | cFTS | 198.79 (282.13) | | 0.001613 | | | NIPT is dominated (more expensive and less effective) |
| | NIPT | 199.89 (283.70) | 1.11 (1.57) | 0.001603 | −0.000010 | −156,700 (−110,621) | |
| Effect: PRL avoided | | | | | | | |
| Model D3 | cFTS | 100.62 (142.81) | | | | | NIPT is more expensive and more effective |
| | NIPT | 101.43 (143.95) | 0.80 (1.14) | 0.000013 | 0.000091 | 8,827 (12,528) | |
| Model D5 | cFTS | 173.98 (246.92) | | 0.000104 | | | NIPT is more expensive and more effective |
| | NIPT | 174.82 (248.11) | 0.84 (1.19) | 0.000013 | 0.000091 | 9,214 (13,030) | |
| Model M3 | cFTS | 126.02 (178.85) | | 0.0000800 | | | NIPT is more expensive and more effective |
| | NIPT | 126.96 (180.20) | 0.95 (1.39) | 0.0000033 | 0.000077 | 12,353 (18,177) | |
| Model M5 | cFTS | 198.79 (282.13) | | 0.0000800 | | | NIPT is more expensive and more effective |
| | NIPT | 199.89 (283.70) | 1.11 (1.57) | 0.0000033 | 0.000077 | 14,366 (20,439) | |
| Effect: QALY | | | | | | | |
| Model D3 | cFTS | 100.62 (142.81) | | 0.9989434 | | | NIPT is more expensive and more effective |
| | NIPT | 101.43 (143.95) | 0.80 (1.14) | 0.9989667 | 0.0000233 | 34,474 (48,844) | |
| Model D5 | cFTS | 173.98 (246.92) | | 0.9915223 | | | NIPT is more expensive and more effective |
| | NIPT | 174.82 (248.11) | 0.84 (1.19) | 0.9915578 | 0.0000560 | 14,990 (21,236) | |
| Model M3 | cFTS | 126.02 (178.85) | | 0.9989341 | | | NIPT is more expensive and more effective |
| | NIPT | 126.96 (180.20) | 0.95 (1.39) | 0.9989515 | 0.0000173 | 54,983 (80,431) | |
| Model M5 | cFTS | 198.79 (282.13) | | 0.9916393 | | | NIPT is dominated (more expensive and less effective) |
| | NIPT | 199.89 (283.70) | 1.11 (1.57) | 0.9915702 | −0.000069 | −16,032 (−22,676) | |

AUD, Australian dollars; cFTS, combined first-trimester screening; ICER, incremental cost-effectiveness ratio; NIPT, noninvasive prenatal testing, PRL, procedure-related loss; QALY, quality-adjusted life-year; T21, trisomy 21; USD, US dollars. ICER refers to the cost/effect. Model 1: 3 health states and a decision tree; model 2: 5 health states and a decision tree; model 3: 3 health states and a microsimulation; model 4: 5 health states and a microsimulation.

compare the impact of including 3 versus 5 health states (i.e., adding termination and spontaneous loss to the model). When using a decision tree and 3 health states, the ICER was approximately USD$35,000 (2023)/QALY, indicating that decision makers may consider funding NIPT. Under a decision tree with 5 health states, NIPT became considerably more cost-effective and thus more likely to be funded, with the ICER decreasing to USD$15,000 (2023)/QALY. Adding 2 health states resulted in small absolute variations in QALYs; however, a small incremental QALY gain led to a relatively large impact on the ICER. The QALY gain was likely driven by the addition of termination as a health state, which reflects the decision made by most women upon receiving a T21 diagnosis.[41,42] Cost-utility analyses of NIPT are sensitive to the number of health states included in the model, and restricting the model to 3 health states is likely to be an oversimplification.

The demonstration model was less sensitive to the number of health states within a CEA. When termination and spontaneous loss were added to the model, there was minimal change in the ICER, most likely due to less differentiation between health states. Within the CEA, spontaneous loss, procedure-related loss, and termination were associated with the same cost, while within the CUA, the same cost was applied to these states, but different utility weights were assigned. An additional finding from this study was that the results and conclusions of the economic models of NIPT were highly dependent on the outcomes being analyzed. When considering cost/T21 detected, 50% of model structures resulted in NIPT being dominated. When considering cost/PRL avoided, none of the model structures found NIPT to be dominated. When considering cost/QALY, 25% of model structures found NIPT to be dominated. This study supports the conclusions made by previous reviews,[11,12] highlighting the challenges arising from the choice of outcome.

A range of modeling techniques (decision tree, Markov model, microsimulation) were identified across included studies. Only a small proportion of studies justified their approach or included a discussion of the possible impacts of their approach on the modeled results. No studies assessed the impacts of the chosen approach within a sensitivity analysis. The current study assessed the impact of using either a decision tree or a microsimulation. The fundamental difference between the 2 approaches was that the decision tree did not consider population heterogeneity, whereas the microsimulation allowed for the incorporation of risks based on maternal age. When looking at cost/T21 detected and using a microsimulation, NIPT was more expensive and less effective and unlikely to be funded. In contrast, a decision tree approach resulted in ICERs below USD$70,000 (2023)/T21 detected, making NIPT more likely to be funded. Microsimulations are recommended for complex interventions because they can incorporate patient heterogeneity and time dependencies.[15] In the context of prenatal screening, patient heterogeneity plays a large role in clinical effectiveness, as the risk of having a child with Down syndrome varies with maternal age.[59] Given the clinical significance of these risks and proven impact on modeled results, we recommend including them within the model.

A previous review of NIPT economic models concluded variations in findings across studies can be primarily attributed to methodological and contextual factors.[11] The current study demonstrates that when employing the same methodology and contextual framework, variations in model structure are associated with large differences in ICER results. However, there is a lack of consensus on how to handle structural uncertainty.[4,5,60] Based on the current work, we created a summary comparison of alternative approaches to managing structural uncertainty, including scenario analysis, model averaging, and value-of-information analysis (Table 7). There is no universal solution, as each available method can have different potential benefits. The most comprehensive option appears to be disease-specific reference models, which have been suggested for complex disease areas.[66,67] They are multiuse models that aim to streamline the model development process and improve model credibility.[63] However, the development of reference models requires a large upfront investment. Prenatal screening presents a complex decision-making area, involving multiple conditions and outcomes. This complexity suggests reference models could be valuable and worth the investment. Further research is needed to assess the feasibility of reference models in the context of prenatal screening and genetic/genomic testing more broadly. The incorporation of reference models into current HTA processes warrants further exploration.

### *Limitations*

The systematic search was limited to databases and HTA Web sites, potentially missing studies from other sources. Given the large number of studies included within the background systematic review, the quality assessment was limited to the Drummond checklist. We consider that this checklist provides an acceptable balance of quality assessment indicators versus efficiency. We aimed to assess the impact of structural uncertainty, rather than the cost-effectiveness of NIPT, and as a

**Table 7** Overview of Methods for Handling Structural Uncertainty and Their Potential Benefits as Judged by the Research Team

| Method | Judgment of Workload to Build the Initial Model | Uncertainty Is Characterized | Single CE Estimate | Practical Guidance on Appropriate Model | Increase Model Transparency | Possible Efficiencies for Future Model Building | Case Studies |
|---|---|---|---|---|---|---|---|
| Scenario analysis<br>*Report alternative models based on different structural assumptions* | High | Yes | | | Yes | | Le 2016,[6] Frederik 2014,[7] Petersohn 2021[64] |
| Model averaging<br>*Weighting outcomes from a set of plausible models based on fit to observed data or expert opinion* | High | Yes | Yes | | Yes | | Petersohn 2021[64] |
| Model parameterization<br>*Adding parameters to the model that define alternative structural choices* | Moderate to high | Yes | Yes | | Yes | | Petersohn 2021[64] |
| Model registries<br>*Store models within an online open access model repository* | Low | | | | Yes | Yes | Pillsbury 2014[65] |
| Value-of-information analysis<br>*Quantifying the value of acquiring additional information* | Moderate to high | Yes | | | Yes | | Strong 2014,[66] Petersohn 2021[64] |
| Model discrepancy analysis<br>*Quantifying the difference between the model evaluated at its "true" input values and the true value of the output quantity* | Moderate to high | Yes | | | Yes | | Strong 2012,[67] James 2021[68] |
| Disease-specific reference models<br>*Multiuse models for use within a disease context* | Very high | | Yes | Yes | Yes | Yes | Drummond 2003,[69] Hiligsmann 2019[70] |

CE, cost-effectiveness.

result a number of simplifications were made: we considered NIPT as a second-line test, over a short time horizon, limited the conditions assessed to T21, and we excluded the impact of intermediate outcomes. Although the models do not include T18 and T13, the results have implications for both conditions. It is likely that when considering additional complexities, structural variations would have a greater impact on results. For example, the impact of uncertain findings will be greater when considering expanded NIPT, and their inclusion is likely to affect CEA results. Similarly, including the possibility of another pregnancy in a longer-term model is likely to create further differences in modeled results. As with all models, we are restricted by the data available, and no model is a perfect reflection of reality. This article demonstrates how structure can affect results but does not demonstrate the impact of all model structures. Instead, it draws on the literature to select the most appropriate structures for comparison.

## Conclusion

This study summarizes the current evidence base for economic evaluations of NIPT and explores the impact of structural uncertainty on modeled results. Most studies conducted cost-effectiveness analyses, and only a small number conducted cost-utility analyses. There is a gap in the literature regarding the valuation of utilities for health outcomes in this context, particularly regarding intermediate outcomes. Published model structures differ in their level of complexity, with key variations in the number of health states and modeling approach. This study demonstrates that variations in model structure are associated with large differences in the ICER and resulting conclusions regarding cost-effectiveness. Policy makers should be aware that structural choices made by modelers may inadvertently affect decisions to support or not support funding for NIPT. The use of context-specific reference models could be explored to provide practical guidance on model selection.

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### ORCID iD

Amber Salisbury https://orcid.org/0000-0003-1557-5918

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## Supplementary materials

### Section A. Search terms

**Table 15. EMBASE search terms**

| No. | Query |
|---|---|
| 1 | high throughput sequencing'/exp OR 'high throughput sequenc*':ti,ab,kw OR 'next generation sequenc*':ti,ab,kw,de OR 'next-generation sequenc*':ti,ab,kw,de OR ngs:ti,ab,kw,de OR 'non-invasive prenatal test*':ti,kw,ab,de OR 'non invasive prenatal test*':ti,kw,de,ab OR nipt:ti,kw,de,ab OR 'noninvasive prenatal test*':ti,ab,de,kw OR metagenomic$:ti,ab,kw,de OR wgs:ti,ab,kw,de OR wes:ti,ab,kw,de OR germline:ti,ab,kw,de OR inherited:ti,ab,kw,de OR inheritable:ti,ab,kw,de OR 'genomic test*':ti,ab,kw,de OR 'gene* test*':ti,ab,kw,de |
| 2 | (('massive* parallel' OR panel OR deep OR 'whole genome' OR exome OR multigene OR 'multi gene' OR monogenic) NEAR/5 (sequenc* OR test*)):ti,ab,kw,de |
| 3 | #1 OR #2 |
| 4 | economic*:ti OR cost*:ti OR utilit*:ti OR 'quality adjusted life year:ti' OR qaly:ti OR 'life year saved':ti OR icer:ti OR value:ti OR hta:ti OR 'health technology assessment':ti OR markov:ti OR 'decision tree':ti OR 'outcome assessment':ti OR 'decision analy*':ti OR 'decision-analy*':ti OR 'cea':ti |
| 5 | #3 AND #4 |
| 6 | #5 NOT (('animal'/exp OR 'nonhuman'/exp OR 'rodent'/exp OR 'animal experiment'/exp OR 'experimental animal'/exp OR rat:ti,ab OR rats:ti,ab OR mouse:ti,ab OR mice:ti,ab OR dog$:ti,ab OR pig$:ti,ab OR porcine:ti,ab OR swine:ti,ab OR chick$:ti,ab) NOT 'human'/exp) AND [2010-2022]/py |
| 7 | #6 NOT ([conference abstract]/lim OR [conference review]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [book]/lim OR 'case report'/de) AND [english]/lim |

**Table 16. MEDLINE search terms**

| No. | Query |
|---|---|
| 1 | High-Throughput Nucleotide Sequencing/ or high throughput sequenc*.mp. or next generation sequenc*.mp. or next-generation sequenc*.mp. or ngs.mp. or non-invasive prenatal test*.mp. or non invasive prenatal test*.mp. or nipt.mp. or noninvasive prenatal test*.mp. or metagenomic$.mp. or wgs.mp. or wes.mp. or germline.mp. or inherited.mp. or inheritable.mp. or genomic test*.mp. or gene* test*.mp. |
| 2 | ((massively parallel or panel or whole genome or exome or multigene or multi gene or monogenic) and (sequenc* or test*)).mp. |
| 3 | 1 or 2 |
| 4 | economic*.ti. or cost*.ti. or utilit*.ti. or quality adjusted life year.ti. or qaly.ti. or life year saved.ti. or icer.ti. or value.ti. or hta.ti. or health technology assessment.ti. or markov.ti. or decision tree.ti. or outcome assessment.ti. or decision analy*.ti. or decision-analy*.ti. or cea.ti. |
| 5 | 3 and 4 |
| 6 | limit 5 to (humans and yr="2010 - 2022") |

**Table 17. SCOPUS search terms**

| No. | Query |
|---|---|
| 1 | TITLE( "high throughput sequenc*" OR "next generation sequenc*" OR ngs OR "non invasive prenatal test*" OR nipt OR "noninvasive prenatal test*" OR metagenomic$ OR wgs OR wes ) OR (TITLE((germline OR inherited OR inheritable OR gene* OR genomic OR "massively parallel" OR panel OR "whole genome" OR exome OR multigene OR "multi gene" OR monogenic) AND (sequenc* OR test*))) AND ( TITLE ( economic* OR cost* OR utilit* ) ) AND ( LIMIT-TO ( PUBYEAR,2022) OR ( LIMIT-TO ( PUBYEAR,2021) OR LIMIT-TO ( PUBYEAR,2020) OR LIMIT-TO ( PUBYEAR,2019) OR LIMIT-TO ( PUBYEAR,2018) OR LIMIT-TO ( PUBYEAR,2017) OR LIMIT-TO ( PUBYEAR,2016) OR LIMIT-TO ( PUBYEAR,2015) OR LIMIT-TO ( PUBYEAR,2014) OR LIMIT-TO ( PUBYEAR,2013) OR LIMIT-TO ( PUBYEAR,2012) OR LIMIT-TO ( PUBYEAR,2011) OR LIMIT-TO ( PUBYEAR,2010) ) AND ( LIMIT-TO ( LANGUAGE,"English" ) ) |

**Table 18. ECON LIT search terms**

| No. | Query |
|---|---|
| 1 | TI(Sequencing) OR TI(sequence analysis) OR TI(genomics) OR TI(genomic testing) OR TI(gene testing) OR AB(Sequencing) OR AB(sequence analysis) OR AB(genomics) OR AB(genomic testing) OR AB(gene testing)<br>Limits: 2010-2022 |

## Section B. Clinical parameters and costs

**Table 19. Clinical parameters for models comparing NIPT against current screening**

| Parameter | Value 1 | Source |
|---|---|---|
| Number of singleton pregnancies | 300,000 | Approximate number of births in Australia (AIHW 2022) |
| T21 viable foetus rate at first trimester | 0.299% | Maxwell 2016 |
| Spontaneous loss between 12 weeks and term (unaffected) | 3% | Avlos 2012 |
| T21 spontaneous pregnancy loss rate between 12 weeks and term | 43% | Morris 1999 |
| T21 termination rate | 93% | Maxwell 2015 |
| % chronic villus sampling | 24% | Norton 2011 |
| % amniocentesis | 76% | Norton 2015 |
| Chronic villus sampling PRL | 0.20% | Salomon 2019 |
| Amniocentesis PRL | 0.30% | Solomon 2019 |
| Overall PRL | 0.276% | Calculation |
| cFTS | | |
| Specificity | 94.6% | Norton 2015 |
| Sensitivity | 78.90% | Norton 2015 |
| Percentage who test high risk | 0.40% | Maxwell 2017 |
| PPV of those who test high risk | 45% | Maxwell 2016 |
| NIPT T21 | | |
| Specificity | 99.9% | Norton 2015 |
| Sensitivity | 100% | Norton 2015 |
| Failure rate | 3% | Norton 2015 |
| Uptake of screening tests | | |
| Uptake of cFTS | 83.60% | Lindquist 2019 |
| Uptake of NIPT after cFTS | 100.00% | Assumption |
| Uptake of invasive testing | | |
| After unreportable NIPT | 100% | Assumption |
| After positive cFTS | 80% | Maxwell 2016 |
| After positive NIPT | 80% | Assumption |
| After high-risk cFTS | 90% | Maxwell 2016 |

Abbreviations: AIHW, Australian Institute of Health and Welfare; cFTS, combined first trimester screening; NIPT, non-invasive prenatal testing; PPV, Positive Predictive Value; PRL, procedure-related loss; T21, trisomy 21.

**Table 20. Costs for models comparing NIPT against current screening (AUD)**

| Service | Fee | 75% benefit | 85% benefit | Chosen value | Source |
|---|---|---|---|---|---|
| cFTS biochemical testing | $39.75 | $29.85 | $33.80 | $33.80 | MBS item 66750 |
| cFTS NT ultrasound | $72.85 | $54.65 | $61.95 | $61.95 | MBS item 55707 |
| Total cFTS | | | | $95.75 | |
| NIPT | $400 | | | $400 | MSAC Public summary document[17] - Proposed MBS item descriptor |
| Amniocentesis | $67.10 | $50.35 | $57.05 | $57.05 | MBS item 16600 |
| Chronic villus sampling | $128.85 | $96.65 | $109.55 | $109.55 | MBS item 16603 |
| Associated ultrasound | $113.55 | $85.20 | $96.55 | $96.55 | MBS item 55054 |
| Pathology cytogenetics | $394.55 | $295.95 | $335.40 | $335.40 | MBS item 73287 |
| Patient Episode Initiation | $2.40 | $1.80 | $2.05 | $2.05 | MBS item 73939 |
| Weighted invasive testing | | | | $517.30 | |
| GP consult | $39.75 | | | $39.75 | MBS item 23 |
| Obstetrician and genetic counselling initial | $91.80 | $68.85 | $78.05 | $78.05 | MBS item 104 |
| Obstetrician and genetic counselling subsequent | $46.15 | $34.65 | $39.25 | $39.25 | MBS item 105 |
| Hospital - Abortion W Gis | $3,250.96 | | | $3,250.96 | DRG O05Z Abortion W Gis |

Abbreviations: cFTS, combined first trimester screening; DRG, Diagnosis-Related Group; Gis, General interventions; GP, general practitioner; MBS, Medicare Benefits Schedule; MSAC, Medical Services Advisory Committee; NIPT, non-invasive prenatal testing; NT, Nuchal Translucency; PRL, procedure-related loss; W, With.

**Table 21. Costs for models comparing NIPT against current screening (converted to USD)**

| Service | Fee | 75% benefit | 85% benefit | Chosen value | Source |
|---|---|---|---|---|---|
| cFTS biochemical testing | $28.01 | $21.03 | $23.82 | $23.82 | MBS item 66750 |
| cFTS NT ultrasound | $51.33 | $38.51 | $43.65 | $43.65 | MBS item 55707 |
| Total cFTS | | | | $67.46 | |
| NIPT | $281.84 | | | $281.84 | MSAC PSD - Proposed MBS item descriptor |
| Amniocentesis | $47.28 | $35.48 | $40.20 | $40.20 | MBS item 16600 |
| Chronic villus sampling | $90.79 | $68.10 | $77.19 | $77.19 | MBS item 16603 |
| Associated ultrasound | $80.01 | $60.03 | $68.03 | $68.03 | MBS item 55054 |
| Pathology cytogenetics | $278.00 | $208.52 | $236.32 | $236.32 | MBS item 73287 |
| Patient Episode Initiation | $1.69 | $1.27 | $1.44 | $1.44 | MBS item 73939 |
| Weighted invasive testing | | | | $364.49 | |
| GP consult | $28.01 | | | $28.01 | MBS item 23 |
| Obstetrician and genetic counselling initial | $64.68 | $48.51 | $54.99 | $54.99 | MBS item 104 |
| Obstetrician and genetic counselling subsequent | $32.52 | $24.41 | $27.66 | $27.66 | MBS item 105 |
| Hospital - Abortion W Gis | $2,290.60 | | | $2,290.60 | DRG O05Z Abortion W Gis |

Abbreviations: cFTS, combined first trimester screening; DRG, Diagnosis-Related Group; Gis, General interventions; GP, general practitioner; MBS, Medicare Benefits Schedule; MSAC, Medical Services Advisory Committee; NIPT, non-invasive prenatal testing; NT, Nuchal Translucency; PSD, Public Summary Document; W, With.

## Section C. Utilities literature search

A systematic review conducted in 2017 and published in a PhD thesis[74] searched for studies eliciting utilities for pregnancy-related health states to inform economic evaluations. A supplementary search was conducted to update the 2017 review. This was undertaken by a member of the research team (AS), with a search span from 2017 to 2023. Quality assessment of the included studies, using the Yepes-Nunez items list for values and preference studies,[75] can be found in (**Table 22**). It was pre-agreed the set of utilities would be chosen based on study quality, applicability to prenatal screening for Down syndrome, and the face validity of utility weights. The utilities presented by Kupperman 2016[34] were employed because they covered the most comprehensive set of relevant health states compared to other available studies (See **Table 24** for values). The Kupperman study presents utilities for pathways, while the current research required utilities for discrete health states. As a result, the utility of a live unaffected birth was anchored to one and the other final health states calculated accordingly. The face validity of the intermediate health states did not seem appropriate, so were not included.

**Section D. Quality assessment**

*Checklist items*[10]

**Was the instrument appropriately administered?**

Was the interviewer trained properly?

Was there a structured protocol for administering the instrument?

Was a structured pre-testing procedure carried out?

Did investigators recruit optimal interviewees?

Did the authors test for participant understanding?

**Was the choice of the instrument optimal?**

Did investigators use a standardized instrument with evidence of validity?

Was the questionnaire used adequately validated for their health condition?

If appropriate, did the authors present probabilities?

Were all relevant outcomes included?

Instrument(s):

Questionnaire(s):

**Was the choice of participants group optimal?**

When patients were respondents, were their health states sufficiently similar?

**Did the patients have previous experience of being involved in a choice related to the value and preference choice under study?**

Were the participants representative of the underlying population?

Was the sample appropriate according to the perspective of the study?

Did the health state presentations have high verisimilitude/were appropriate?

Did the authors address the literature bearing on the patients' views and experiences of the health conditions?

Did the investigators justify their choice of health state: patients' own vs hypothetical scenarios?

**Were the methods and results described, analyzed, and presented optimally?**

Were methods applied in the study clearly described?

Did the authors report the results clearly?

Was the information presented convincingly?

Did the authors adequately justify any omissions of data collected in the analyses?

Did authors conduct the appropriate statistical analyses?

**Do results suggest patient understanding was adequate?**

Were the health states rated consistently?

Did the authors address patient characteristics that may have a strong association with values and preferences?

**Was a subgroup analysis conducted optimally?**

Did the authors examine possible associations between patient characteristics and values and preferences?

**Table 22. Quality assessment for utility studies suing the Yepes-Nunez items list for values and preference studies**

| Author | Year | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Kupperman | 2016 | ? | Y | ? | Y | ? | NR | NR | Y | Y | Y | ? | Y | Y | Y | Y | Y | Y | Y | NR | Y | Y | Y | Y |
| Deverill | 2006 | ? | Y | ? | Y | ? | NR | NR | N | Y | N | ? | Y | Y | Y | Y | Y | Y | Y | NR | Y | Y | Y | NR |
| Kupperman | 2004 | ? | Y | ? | Y | ? | NR | NR | ? | Y | Y | ? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | NR |
| Grobman | 2002 | Y | Y | Y | Y | ? | NR | NR | ? | ? | Y | ? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Kupperman | 2000 | Y | Y | ? | Y | Y | NR | NR | Y | Y | Y | ? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | NR |
| Verp | 1995 | ? | ? | ? | N | ? | NR | NR | Y | ? | Y | ? | ? | ? | Y | Y | Y | Y | Y | NR | Y | NR | NR | NR |
| Heckerling | 1994 | Y | Y | ? | Y | Y | NR | NR | ? | ? | Y | ? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Pauker | 1987 | Y | Y | ? | Y | Y | NR | NR | Y | Y | Y | ? | Y | Y | Y | Y | Y | Y | Y | ? | Y | Y | Y | Y |

Abbreviaitons: NR; not relevant; Y; yes, ?; unclear.

## Section E. Literature review results

**Table 23. Basic characteristics of included studies**

| Study ID | Country | Study type | Perspective | Time horizon | Clinical condition | Cost discount rate | Outcome discount rate | Primary outcome measure(s) |
|---|---|---|---|---|---|---|---|---|
| Anh (2021) | Vietnam | CUA | Societal | Lifetime | T21 | None | 3.0% | QALY of pregnant woman |
| Ayres (2015) | Australia | CEA | Healthcare funder + patient | Pregnancy to birth | T21 | None | None | T21 detected and PRL avoided |
| Bayón (2019) | Spain | CEA | healthcare funder | Pregnancy to birth | T21 | None | None | T21 detected |
| Benn (2015) | USA | Threshold analysis | Healthcare funder + patient | Lifetime | T21, T18, and T13 and monosomy X | None | None | Cases detected and PRL avoided |
| Beulen (2014) | The Netherlands | CEA | Healthcare funder + patient | Pregnancy to birth | T21 | None | None | T21 detected and PRL avoided |
| Colosi (2017) | Italy | Cost and consequence | Healthcare funder | Pregnancy to birth | T21, T18, and T13 | None | None | Cases detected and PRL avoided |
| Crimmins (2017) | USA | Threshold analysis | Healthcare funder + patient | Pregnancy to birth | T21 | None | None | T21 detected, PRL avoided and number of false positives |

| Study ID | Country | Study type | Perspective | Time horizon | Clinical condition | Cost discount rate | Outcome discount rate | Primary outcome measure(s) |
|---|---|---|---|---|---|---|---|---|
| Cuckle (2013) | USA | CEA | healthcare funder | Pregnancy to birth | T21 | None | None | T21 detected |
| Fairbrother (2016) | USA | Threshold analysis | Healthcare funder + patient | Pregnancy to birth | T21, T18, and T13 | None | None | Cases detected |
| Garfield (2012) | USA | Cost and consequence | healthcare funder | Pregnancy to birth | T21, T18, and T13 | None | None | Cases detected and PRL avoided |
| Gyselaers (2015) | Belgium | Cost and consequence | healthcare funder | Pregnancy to birth | T21 | None | None | T21 detected |
| Hopkins (2020) | USA | CEA | healthcare funder | Pregnancy to birth | T21 | None | None | T21 detected, PRL avoided, number of unnecessary invasive tests |
| HQO (2019) | Canada | CEA | healthcare funder | Pregnancy to birth | T21, T18, T13, sex chromosome aneuploidies, and microdeletions | None | None | Cases detected |
| Huang (2020) | Canada | Cost and consequence | healthcare funder | Pregnancy to birth | T21 | None | None | T21 detected |
| IHE (2014) | Canada | CEA | healthcare funder | Pregnancy to birth | T21 | None | None | Cases detected and cases correctly diagnosed |
| Kaimal (2015) | USA | CUA | healthcare funder | Lifetime | T21, T18, and T13 | 3.0% | 3.0% | QALY of pregnant woman |

| Study ID | Country | Study type | Perspective | Time horizon | Clinical condition | Cost discount rate | Outcome discount rate | Primary outcome measure(s) |
|---|---|---|---|---|---|---|---|---|
| KCE (2014) | Belgium | CEA | Healthcare funder + patient | Pregnancy to birth | T21 | None | None | T21 detected |
| Kostenko (2019) | Belgium | CEA | healthcare funder | Pregnancy to birth | T21, T18, and T13 | 5.0% | None | Cases detected |
| Maxwell (2017) | Australia | CEA | healthcare funder | Pregnancy to birth | T21 | None | None | T21 detected |
| Morris (2014) | UK | Cost and consequence | healthcare funder | Pregnancy to birth | T21 | None | None | T21 detected and PRL avoided |
| MSAC (2019) | Australia | CEA | Healthcare funder | Pregnancy to birth | T21, T18, and T13 | None | None | Cases detected |
| Neyt (2014) | Belgium | CEA | healthcare funder | Pregnancy to birth | T21 | None | None | T21 detected |
| Nshimyumukiza (2018) | Canada | CEA | healthcare funder | Pregnancy to birth | T21, T18, and T13 | None | None | T21 detected |
| Ökem (2017) | Turkey | CEA | Healthcare funder + patient | Pregnancy to birth | T21 | None | None | T21 detected and PRL avoided |
| Okun (2014) | Canada | CEA | healthcare funder | Pregnancy to birth | T21 | None | None | T21 detected |
| O'Leary (2013) | Australia | CEA | healthcare funder | Pregnancy to birth | T21 | None | None | T21 detected |

| Study ID | Country | Study type | Perspective | Time horizon | Clinical condition | Cost discount rate | Outcome discount rate | Primary outcome measure(s) |
|---|---|---|---|---|---|---|---|---|
| Shang (2021) | China | CEA | healthcare funder | Pregnancy to birth | T21 | None | None | T21 averted |
| Song (2013) | USA | CEA | Societal | First 5 years of life | T21 | 3.0% | None | T21 detected |
| Walker (2014) | USA | CEA | Societal | Lifetime | T21 | None | None | T21 detected |
| Walker (2015) | USA | CEA | Societal and funder | Lifetime | T21, T18, and T13 | 3.0% | None | Cases detected |
| Wanapirak (2019)[51] | Thailand | CBA | Societal and funder | Lifetime | T21 | None | None | T21 averted |
| Xie (2020) | Canada | CEA | healthcare funder | Pregnancy to birth | T21 | None | None | T21 detected |
| Xu (2019) | China | CEA | Societal | Pregnancy to birth | T21, T18, T13, sex chromosome aneuploidies, and microdeletions | None | None | T21 averted |
| Zhang (2019) | Canada | CUA | Healthcare funder + patient | Pregnancy until 18yrs old | T21 | 3.0% | 3.0% | QALY of pregnant woman |

Abbreviations: CBA, cost-benefit analysis; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; PRL, procedure-related loss; QALY, quality adjusted life year.

**Table 24. Identified cost utility analyses and utility weights**

| Pregnancy scenario | Kaimal 2015[20] | | | | Zhang 2019[21] | | | | Anh 2021[45] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean utility | (SD) | Source | Method | Mean utility | (SD) | Source | Method | Mean utility | CI | Source | Method |
| **One screening test with low-risk results** | | | | | | | | | | | | |
| Unspecified screening test, low-risk result | 0.931 | 0.154 | Kaimal 2015[20] | TTO | 0.931 | 0.154 | Kupperman 2016 | TTO | NR | NR | NR | NR |
| **Diagnostic testing with normal results** | | | | | | | | | | | | |
| cfDNA, no result; CVS or amniocentesis, normal result | 0.928 | 0.15 | Kaimal 2015[20] | TTO | 0.921 | 0.161 | Kupperman 2016 | TTO | 0.923 | 0.62;1 | Harris 2004 | TTO |
| MMS, increased risk result; CVS or amniocentesis, normal result | 0.925 | 0.161 | Kaimal 2015[20] | TTO | 0.921 | 0.161 | Kupperman 2016 | TTO | 0.923 | 0.62;1 | Harris 2004 | TTO |
| Straight to CVS or amniocentesis (with no prior screening), normal result | 0.921 | 0.161 | Kaimal 2015[20] | TTO | 0.921 | 0.161 | Kupperman 2016 | TTO | 0.923 | 0.62;1 | Harris 2004 | TTO |
| **Two screening tests with differing results** | | | | | | | | | | | | |
| MMS alone, increased risk result; cfDNA, low-risk result | 0.89 | 0.199 | Kaimal 2015[20] | TTO | NR | NR | NR | NR | NR | NR | NR | NR |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MMS and cfDNA together, MMS increased risk result and cfDNA low-risk result | 0.85 | 0.229 | Kaimal 2015[20] | TTO | NR | NR | NR | NR | NR | NR | NR | NR |
| **Pregnancy termination in the context of abnormal results** | | | | | | | | | | | | |
| One unspecified screening test, increased risk result; CVS or amniocentesis, abnormal result; terminate | 0.771 | 0.284 | Kaimal 2015 unpublished | TTO | 0.771 | 0.284 | Kupperman 2016[34] | TTO | 0.836 | 0.4,1.0 | Harris 2004 | TTO |
| MMS alone, increased risk result; cfDNA test, increased risk result; CVS or amniocentesis, abnormal result; terminate | 0.771 | 0.268 | Kaimal 2015 unpublished | TTO | 0.771 | 0.284 | Kupperman 2016[34] | TTO | 0.836 | 0.4,1.0 | Harris 2004 | TTO |
| Straight to CVS or amniocentesis, abnormal result; terminate | 0.725 | 0.294 | Kaimal 2015 unpublished | TTO | NR | NR | NR | NR | 0.836 | 0.4,1.0 | Harris 2004 | TTO |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Pregnancy termination in the context of VUS results** | | | | | | | | | | | | |
| Unspecified screening test, increased risk result; CVS or amniocentesis, VUS; terminate | 0.762 | 0.29 | Kaimal 2015 unpublished | TTO | NR | NR | NR | NR | 0.836 | 0.4,1.0 | Harris 2004 | TTO |
| Straight to CVS or amniocentesis, VUS; terminate | 0.694 | 0.3 | Kaimal 2015 unpublished | TTO | NR | NR | NR | NR | 0.836 | 0.4,1.0 | Harris 2004 | TTO |
| **Miscarriage** | | | | | | | | | | | | |
| Unspecified screening test, increased risk result; CVS or amniocentesis, miscarriage | 0.744 | 0.285 | Kaimal 2015 unpublished | TTO | NR | NR | NR | NR | 0.76 | 0.68;0.94 | Kuppermann 2000 | TTO |
| Straight to CVS or amniocentesis, procedure related miscarriage | 0.663 | 0.28 | Kaimal 2015 unpublished | TTO | NR | NR | NR | NR | 0.76 | 0.68;0.94 | Kuppermann 2000 | TTO |
| Spontaneous loss (affected) | NR | | | | 0.744 | 0.285 | Kupperman 2016 | TTO | 0.76 | 0.68;0.94 | Kuppermann 2000 | TTO |
| Spontaneous loss (unaffected) | NR | | | | 0.744 | 0.285 | Kupperman 2016 | TTO | 0.76 | 0.68;0.94 | Kuppermann 2000 | TTO |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Pregnancy continuation in the context of screen positive results with no further testing or abnormal diagnostic test results** | | | | | | | | | | | | |
| cfDNA, no result; no further testing, continue pregnancy | 0.763 | 0.281 | Kaimal 2015 unpublished | TTO | NR | NR | NR | NR | NR | NR | NR | NR |
| MMS, increased risk result; no further testing, continue pregnancy | 0.756 | 0.258 | Kaimal 2015 unpublished | TTO | NR | NR | NR | NR | NR | NR | NR | NR |
| MMS, increased risk result; cfDNA, increased risk result; no further testing, continue pregnancy | 0.682 | 0.27 | Kaimal 2015 unpublished | TTO | NR | NR | NR | NR | 0.69 | 0.54;0.88 | Kuppermann 2000 | TTO |
| Unspecified screening test, increased risk result; CVS or amniocentesis, abnormal result; continue pregnancy | 0.655 | 0.282 | Kaimal 2015 unpublished | TTO | NR | NR | NR | NR | 0.69 | 0.54;0.88 | Kuppermann 2000 | TTO |
| **Pregnancy continuation in the context of VUS** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Unspecified screening test, increased risk result; CVS or amniocentesis, VUS; continue pregnancy | 0.806 | 0.234 | Kaimal 2015 unpublished | TTO | NR | NR | NR | NR | NR | NR | NR | NR |
| **Long term outcomes** | | | | | | | | | | | | |
| Baby with Down syndrome or another intellectual disability | 0.48 | 0.305 | Kaimal 2015 unpublished | TTO | 0.48 | 0.305 | Kupperman 2016 | TTO | 0.55 | 0.28;0.82 | Mok 2014 | Multi attribute questionnaire - HUI3 |
| Baby with trisomy 13 or 18 | 0.495 | 0.323 | Kaimal 2015 unpublished | TTO | NR | NR | NR | NR | NR | NR | NR | NR |
| Baby with VUS | 0.737 | 0.28 | Kaimal 2015 unpublished | TTO | NR | NR | NR | NR | NR | NR | NR | NR |
| Pregnancy loss with repeat pregnancy and birth of a healthy baby 2 years later | 0.88 | 0.178 | Kaimal 2015 unpublished | TTO | 0.88 | 0.178 | Kupperman 2016 | TTO | NR | NR | NR | NR |
| Pregnancy loss with no future pregnancy | 0.59 | 0.313 | Kaimal 2015 unpublished | TTO | 0.59 | 0.313 | Kupperman 2016 | TTO | NR | NR | NR | NR |

Abbreviations: cfDNA, cell-free DNA; CI, confidence interval; CVS, chorionic villus sampling; HUI3, Health Utilities Index Mark 3; MMS, maternal marker screening; NR, not reported; SD, standard deviation; TTO, time trade off; VUS, variant of uncertain significance.

## Section F. Sensitivity analysis results

**Table 25. One-way sensitivity analysis: models D3 and D5 (AUD)**

| Param. | Base (%) | Test (%) | Source | model D3 | | | | | | model D5 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Cost/T21 (AUD) | | Cost/PRL avoided (AUD) | | Cost/QALY gained (AUD) | | Cost/T21 (AUD) | | Cost/PRL avoided (AUD) | | Cost/QALY gained (AUD) | |
| | | | | Low value | High value | Low value | High value | Low value | High value | Low value | High value | Low value | High value | Low value | High value |
| **Test characteristics** | | | | | | | | | | | | | | | |
| NIPT sens. | 100.0 | 90.7, 100.0 | Norton 2015[11] | -8,181 | 93,141 | 11,599 | 12,527 | 46,158 | 49,590 | -6,644 | 96,873 | 11,694 | 12,855 | 20,546 | 21,188 |
| NIPT spec. | 99.9 | 99.9, 100.0 | Norton 2015[11] | 93,141 | 91,600 | 12,527 | 12,307 | 49,590 | 48,731 | 96,873 | 95,332 | 12,855 | 12,635 | 21,188 | 20,842 |
| cFTS sens. | 78.9 | 62.7, 90.4 | Norton 2015[11] | 97,991 | 90,721 | 10,566 | 13,919 | 41,781 | 55,132 | 101,852 | 94,389 | 10,848 | 14,280 | 20,347 | 21,670 |
| cFTS spec. | 94.6 | 94.2, 94.9 | Norton 2015[11] | 94,268 | 92,296 | 11,765 | 13,181 | 46,561 | 52,189 | 98,045 | 95,994 | 10,173 | 13,524 | 20,792 | 21,501 |
| **Uptake** | | | | | | | | | | | | | | | |
| cFTS | 83.6 | 60.0, 100.0 | Maxwell 2011[88] | 93,131 | 93,141 | 12,527 | 12,527 | 49,590 | 49,590 | 96,873 | 96,873 | 12,855 | 12,855 | 21,188 | 21,188 |
| NIPT | 100.0 | 76.0, 100.0 | HQO 2019[13] | 9,692 | 93,141 | -38,371 | 12,527 | -151,633 | 49,590 | 11,351 | 96,873 | -38,371 | 12,855 | -217,023 | 21,188 |
| Invasive test after cFTS | 80.0 | 40.0, 100.0 | Lindquist 2019[73] | 13,498 | 9,666 | 275,459 | -31,561 | 11,001,646 | -124,281 | 15,238 | 11,311 | 310,556 | -37,062 | 117,091 | -135,398 |
| Invasive test after high cFTS | 90.0 | 40.0, 100.0 | Lindquist 2019[73] | 66,804 | 97,290 | 7,137 | 13,641 | 28,529 | 53,943 | 71,014 | 100,946 | 7,418 | 13,979 | 12,589 | 22,922 |
| Invasive test after NIPT | 80.0 | 40.0, 100.0 | Lindquist 2019 [73] | -985 | 3,407 | 7,932 | 14,907 | 32,248 | 58,163 | 708 | 5,196 | -5,781 | 22,508 | 27,108 | 21,806 |

Abbreviations**:** AUD, Australian Dollar; cFTS, combined first trimester screening; NIPT, non-invasive prenatal testing; Param, parameter; PRL, procedure-related loss; sens., sensitivity; spec., specificty; QALY, Quality-adjusted life year; T21, Trisomy 21.

**Table 26. One-way sensitivity analysis: models D3 and D5 (converted to USD)**

| Param. | Base (%) | Test (%) | Source | model D3 | | | | | | model D5 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Cost/T21 (USD) | | Cost/PRL avoided (USD) | | Cost/QALY gained (USD) | | Cost/T21 (USD) | | Cost/PRL avoided (USD) | | Cost/QALY gained (USD) | |
| | | | | Low value | High value | Low value | High value | Low value | High value | Low value | High value | Low value | High value | Low value | High value |
| **Test characteristics** | | | | | | | | | | | | | | | |
| NIPT sens. | 100.0 | 90.7, 100.0 | Norton 2015[11] | -5,764 | 65,626 | 8,173 | 8,826 | 32,523 | 34,941 | 4,681 | 68,256 | 8,240 | 9,058 | 14,477 | 14,929 |
| NIPT spec. | 99.9 | 99.9, 100.0 | Norton 2015[11] | 65,626 | 64,541 | 8,826 | 8,671 | 34,941 | 34,335 | 68,256 | 67,170 | 9,058 | 8,903 | 14,929 | 14,685 |
| cFTS sens. | 78.9 | 62.7, 90.4 | Norton 2015[11] | 69,044 | 63,921 | 7,445 | 9,807 | 29,439 | 38,846 | 71,764 | 66,506 | 7,643 | 10,062 | 14,336 | 15,269 |
| cFTS spec. | 94.6 | 94.2, 94.9 | Norton 2015[11] | 66,421 | 65,031 | 8,290 | 9,287 | 32,807 | 36,772 | 69,082 | 67,637 | 7,168 | 9,529 | 14,650 | 15,149 |
| **Uptake** | | | | | | | | | | | | | | | |
| cFTS | 83.6 | 60.0, 100.0 | Maxwell 2011[88] | 65,619 | 65,626 | 8,826 | 8,826 | 34,941 | 34,941 | 68,256 | 68,256 | 9,058 | 9,058 | 14,929 | 14,929 |
| NIPT | 100.0 | 76.0, 100.0 | HQO 2019[13] | 6,829 | 65,626 | -27,036 | 8,826 | -106,839 | 34,941 | 7,998 | 68,256 | -24,362 | 9,058 | -152,913 | 14,929 |
| Invasive test after cFTS | 80.0 | 40.0, 100.0 | Lindquist 2019[73] | 9,511 | 6,811 | 194,086 | -22,238 | 7,751,678 | -87,567 | 10,737 | 7,970 | 218,815 | 26,114 | 82,501 | -95,400 |
| Invasive test after high cFTS | 90.0 | 40.0, 100.0 | Lindquist 2019[73] | 47,070 | 68,550 | 5,029 | 9,611 | 20,101 | 38,008 | 50,036 | 71,126 | 5,227 | 9,849 | 8,870 | 16,151 |
| Invasive test after NIPT | 80.0 | 40.0, 100.0 | Lindquist 2019 [73] | -694 | 2,401 | 5,589 | 10,503 | 22,722 | 40,981 | 499 | 3,661 | -4,073 | 15,859 | 19,100 | 15,364 |

Abbreviations**:** AUD, Australian Dollar; cFTS, combined first trimester screening; NIPT, non-invasive prenatal testing; Param, parameter; PRL, procedure-related loss; sens., sensitivity; spec., specificty; QALY, Quality-adjusted life year; T21, Trisomy 21.

**Table 27. One-way sensitivity analysis: models M3 and M5 (AUD)**

| Param. | Base (%) | Test (%) | Source | model M3 | | | | | | model M5 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Cost/T21 (AUD) | | Cost/PRL avoided (AUD) | | Cost/QALY gained (AUD) | | Cost/T21 (AUD) | | Cost/PRL avoided (AUD) | | Cost/QALY gained (AUD) | |
| | | | | Low value | High value | Low value | High value | Low value | High value | Low value | High value | Low value | High value | Low value | High value |
| **Test characteristics** | | | | | | | | | | | | | | | |
| NIPT sens. | 100.0 | 90.7, 100.0 | Norton 2015[11] | -9,196 | -139,361 | 17,192 | 18,177 | 76,073 | 80,431 | -8,346 | -156,700 | -15,637 | -20,439 | -15,547 | -22,676 |
| NIPT spec. | 99.9 | 99.9, 100.0 | Norton 2015[11] | -139,361 | -139,361 | 18,177 | 17,959 | 80,431 | 79,465 | -156,700 | -155,026 | -20,439 | -20,220 | -22,676 | -22,433 |
| cFTS sens. | 78.9 | 62.7, 90.4 | Norton 2015[11] | -61,377 | -152,657 | 20,495 | 20,576 | 70,846 | 88,105 | -70,046 | -166,744 | -22,191 | -22,413 | -25,684 | -20,211 |
| cFTS spec. | 94.6 | 94.2, 94.9 | Norton 2015[11] | -143,055 | -132,124 | 18,177 | 18,017 | 75,160 | 80,205 | -163,644 | -149,463 | -19,636 | -20,381 | -23,392 | -21,365 |
| **Uptake** | | | | | | | | | | | | | | | |
| cFTS | 83.6 | 60.0, 100.0 | Maxwell 2011[88] | -286,242 | -126,617 | 16,838 | 18,758 | 78,166 | 86,178 | -299,246 | -146,122 | -17,602 | -21,647 | -21,657 | -21,396 |
| NIPT | 100.0 | 76.0, 100.0 | HQO 2019[13] | 8,657 | -139,362 | -41,401 | 18,177 | -183,191 | 80,432 | 9,356 | -156,700 | 44,739 | -20,439 | 37,063 | -22,676 |
| Invasive test after cFTS | 80.0 | 40.0, 100.0 | Lindquist 2019[73] | 3,339 | 8,986 | 73,458 | -33,699 | 1,203,335 | 143,742 | 15,308 | 10,205 | -313,823 | 38,270 | 1,123,474 | 44,839 |
| Invasive test after high cFTS | 90.0 | 40.0, 100.0 | Lindquist 2019[73] | -94,519 | 150,151 | 12,328 | 19,585 | 54,551 | 86,659 | -124,860 | 166,405 | -16,286 | -21,705 | -15,736 | -24,381 |
| Invasive test after NIPT | 80.0 | 40.0, 100.0 | Lindquist 2019 [73] | -1,269 | 4,145 | 12,916 | 22,042 | 57,151 | 91,721 | 272 | 6,339 | 2,773 | -33,716 | 1,991 | -49,335 |

Abbreviations**:** AUD, Australian Dollar; cFTS, combined first trimester screening; NIPT, non-invasive prenatal testing; Param, parameter; PRL, procedure-related loss; sens., sensitivity; spec., specificty; QALY, Quality-adjusted life year; T21, Trisomy 21.

**Table 28. One-way sensitivity analysis: models M3 and M5 (converted to USD)**

| Param. | Base (%) | Test (%) | Source | model M3 | | | | | | model M5 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Cost/T21 (USD) | | Cost/PRL avoided (USD) | | Cost/QALY gained (USD) | | Cost/T21 (USD) | | Cost/PRL avoided (USD) | | Cost/QALY gained (USD) | |
| | | | | Low value | High value | Low value | High value | Low value | High value | Low value | High value | Low value | High value | Low value | High value |
| **Test characteristics** | | | | | | | | | | | | | | | |
| NIPT sens. | 100.0 | 90.7, 100.0 | Norton 2015[11] | -6,479 | -98,193 | 12,113 | 12,807 | 53,600 | 56,671 | -5,881 | -110,410 | -11,018 | -14,401 | -10,954 | -15,977 |
| NIPT spec. | 99.9 | 99.9, 100.0 | Norton 2015[11] | -98,193 | -98,193 | 12,807 | 12,654 | 56,671 | 55,990 | -110,410 | -109,230 | -14,401 | -14,247 | -15,977 | -15,806 |
| cFTS sens. | 78.90 | 62.7, 90.4 | Norton 2015[11] | -43,246 | -107,561 | 14,441 | 14,498 | 49,918 | 62,078 | -49,354 | -117,487 | -15,636 | -15,792 | -18,097 | -14,241 |
| cFTS spec. | 94.6 | 94.2, 94.9 | Norton 2015[11] | -100,795 | -93,094 | 12,807 | 12,695 | 52,957 | 56,512 | -115,302 | -105,311 | -13,835 | -14,360 | -16,482 | -15,054 |
| **Uptake** | | | | | | | | | | | | | | | |
| cFTS | 83.6 | 60.0, 100.0 | Maxwell 2011[88] | -201,684 | -89,213 | 11,864 | 13,217 | 55,075 | 60,720 | -210,846 | -102,956 | -12,402 | -15,252 | -15,259 | -15,075 |
| NIPT | 100.0 | 76.0, 100.0 | HQO 2019[13] | 6,100 | -98,193 | -29,171 | 12,807 | -129,075 | 56,672 | 6,592 | -110,410 | 31,523 | -14,401 | 26,114 | -15,977 |
| Invasive test after cFTS | 80.0 | 40.0, 100.0 | Lindquist 2019[73] | 2,353 | 6,331 | 51,758 | -23,744 | 847,861 | 101,280 | 10,786 | 7,190 | -221,117 | 26,965 | 791,591 | 31,593 |
| Invasive test after high cFTS | 90.0 | 40.0, 100.0 | Lindquist 2019[73] | -66,597 | 105,795 | 8,686 | 13,799 | 38,436 | 61,059 | -87,975 | 117,248 | -11,475 | -15,293 | -11,087 | -17,179 |
| Invasive test after NIPT | 80.0 | 40.0, 100.0 | Lindquist 2019 [73] | -894 | 2,921 | 9,101 | 15,531 | 40,268 | 64,626 | 192 | 4,466 | 1,954 | -23,756 | 1,403 | -34,761 |

Abbreviations**:** AUD, Australian Dollar; cFTS, combined first trimester screening; NIPT, non-invasive prenatal testing; Param, parameter; PRL, procedure-related loss; sens., sensitivity; spec., specificty; QALY, Quality-adjusted life year; T21, Trisomy 21

## Section G. Probabilistic sensitivity analysis

**Table 29. Probabilistic sensitivity analysis**

| Threshold | model D3 | | | model D5 | | |
|---|---|---|---|---|---|---|
| | **T21** | **PRL avoided** | **QALY gained** | **T21** | **PRL avoided** | **QALY gained** |
| 25,000 AUD 2023/outcome *(17,614 USD 2023)* | NIPT will be funded in 17.8% of cases | NIPT will be funded in 74.6% of cases | NIPT will be funded in 42.5% of cases | NIPT will be funded in 23.9% of cases | NIPT will be funded in 84.4% of cases | NIPT will be funded in 57% of cases |
| 50,000 AUD 2023/outcome *(35,300 USD 2023)* | cFTS will be funded in 21.6% of cases | NIPT funded in 93% of cases | NIPT will be funded in 44.6% of cases | NIPT will be funded in 31.7% of cases | NIPT will be funded in 95% of cases | NIPT will be funded in 76% of cases |
| 100,000 AUD 2023/outcome *(70,459 USD 2023)* | cFTS will be funded in 23.4% of cases | NIPT funded in 99.5% of cases | NIPT will be funded in 75.6% of cases | NIPT will be funded in 35%of cases | NIPT will be funded in 99.6% of cases | NIPT will be funded in 94% of cases |

Abbreviations: AUD, Australian Dollar; cFTS, combined first trimester screening; NIPT, non-invasive prenatal testing; PRL, procedure-related loss; QALY, Quality-adjusted life year; T21, Trisomy 21; USD, United States Dollar.

**Table 30. Probabilistic sensitivity analysis**

| Threshold | model M3 | | | model M5 | | |
|---|---|---|---|---|---|---|
| | **T21** | **PRL avoided** | **QALY gained** | **T21** | **PRL avoided** | **QALY gained** |
| 25,000 AUD 2023/outcome *(17,614 USD 2023)* | NIPT will be funded in 0% of cases | NIPT will be funded in 96% of cases | NIPT will be funded in 0% of cases | NIPT will be funded in 0% of cases | NIPT will be funded in 95% of cases | NIPT will be funded in 0% of cases |
| 50,000 AUD 2023/outcome *(35,300 USD 2023)* | NIPT will be funded in 0% of cases | NIPT will be funded in 100% of cases | NIPT will be funded in 74% of cases | NIPT will be funded in 0% of cases | NIPT will be funded in 100% of cases | NIPT will be funded in 0% of cases |
| 100,000 AUD 2023/outcome *(70,459 USD 2023)* | NIPT will be funded in 26% of cases | NIPT will be funded in 100% of cases | NIPT will be funded in 95% of cases | NIPT will be funded in 26% of cases | NIPT will be funded in 100% of cases | NIPT will be funded in 0% of cases |

Abbreviations: AUD, Australian Dollar; cFTS, combined first trimester screening; NIPT, non-invasive prenatal testing; PRL, procedure-related loss; QALY, Quality-adjusted life year; T21, Trisomy 21; USD, United States Dollar.

## Section H. Model structures

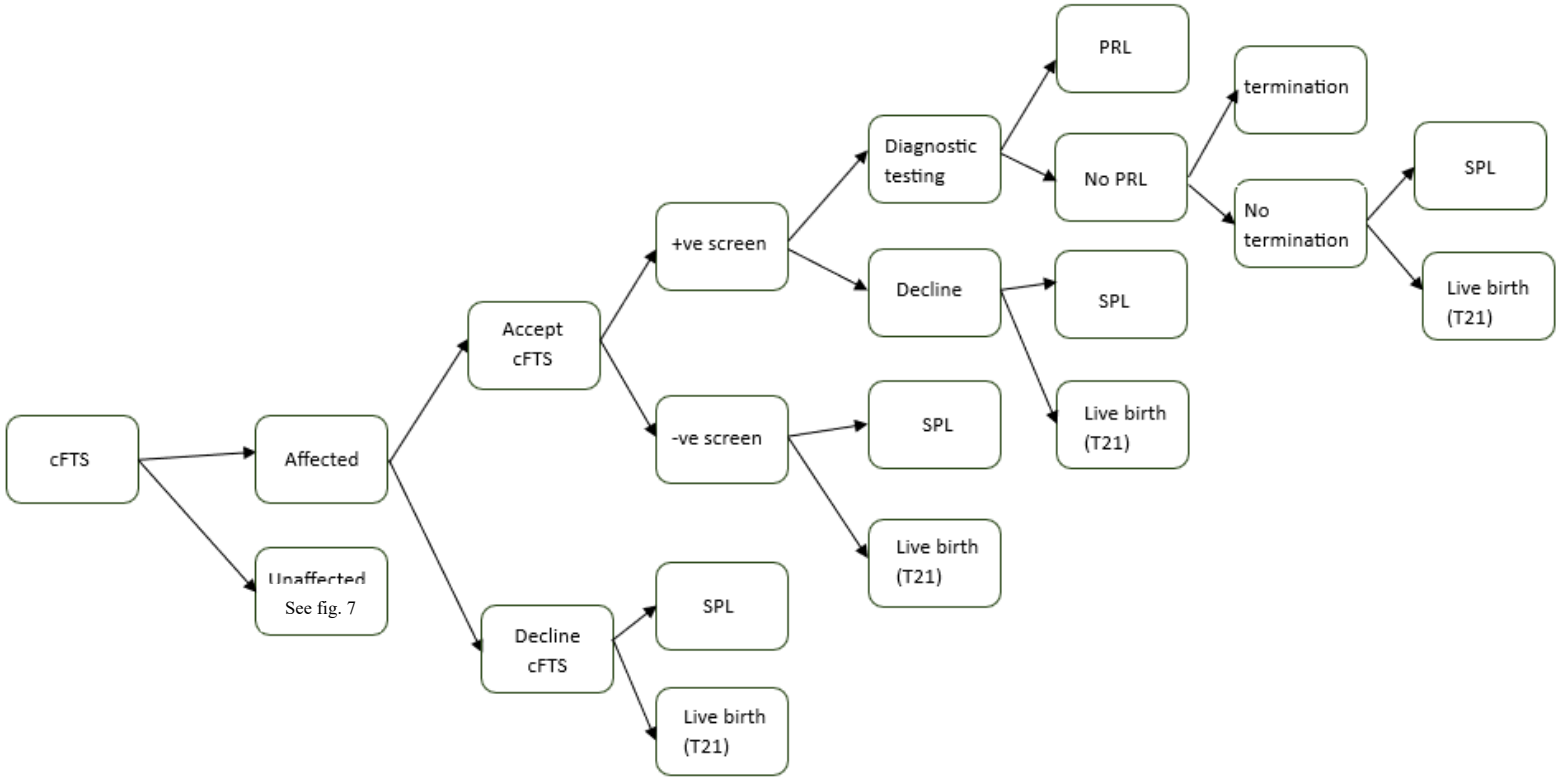


**Figure 6. cFTS affected pathway (all health states included)**

Abbreviations: cFTS, combined first trimester screening; +ve, positive; NIPT, non-invasive prenatal testing; PRL, procedure-related loss; SPL, spontaneous loss; T21, trisomy 21; -ve, negative.

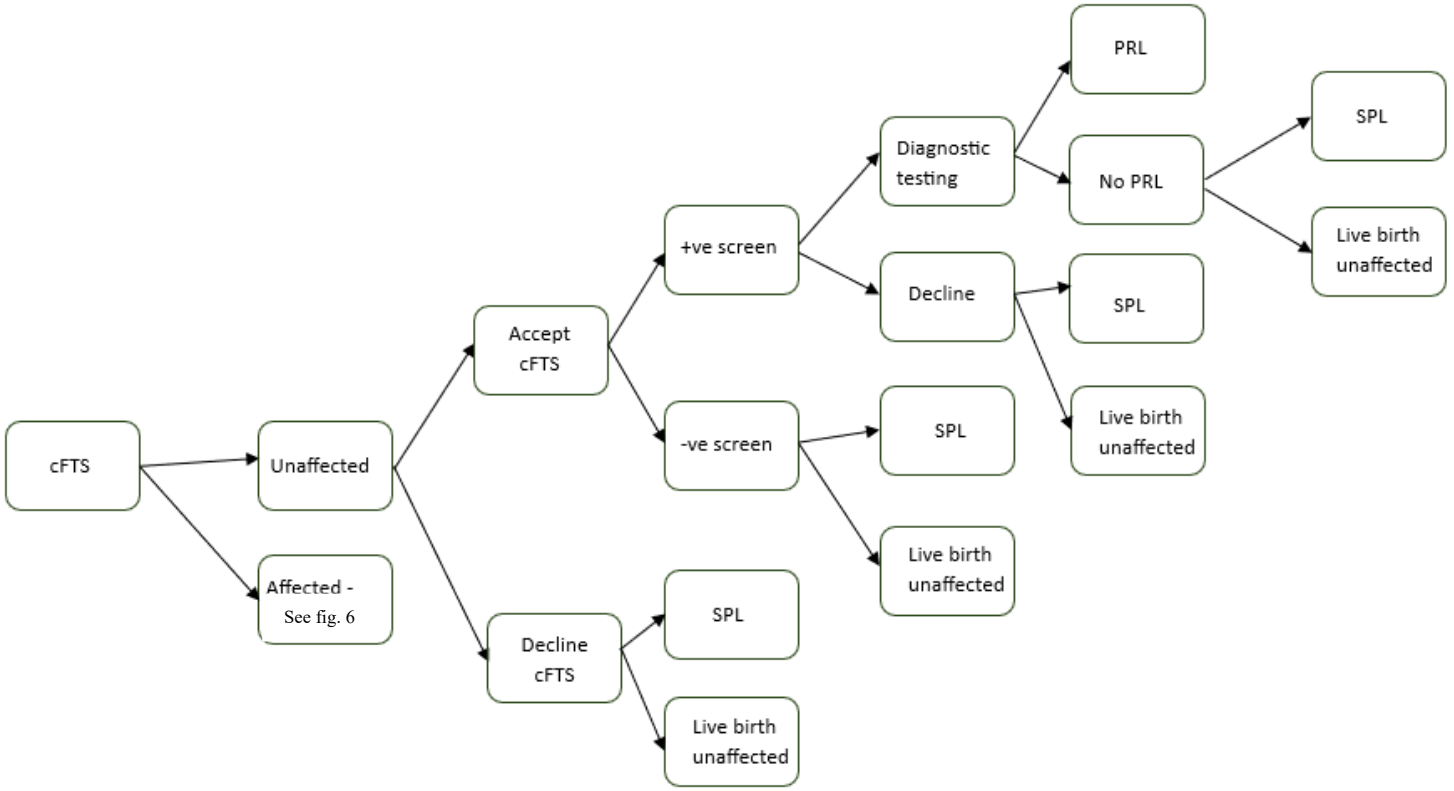


**Figure 7. cFTS unaffected pathway (all health states included)**

Abbreviations: cFTS, combined first trimester screening; +ve, positive; NIPT, non-invasive prenatal testing; PRL, procedure-related loss; SPL, spontaneous loss; T21, trisomy 21; -ve, negative.

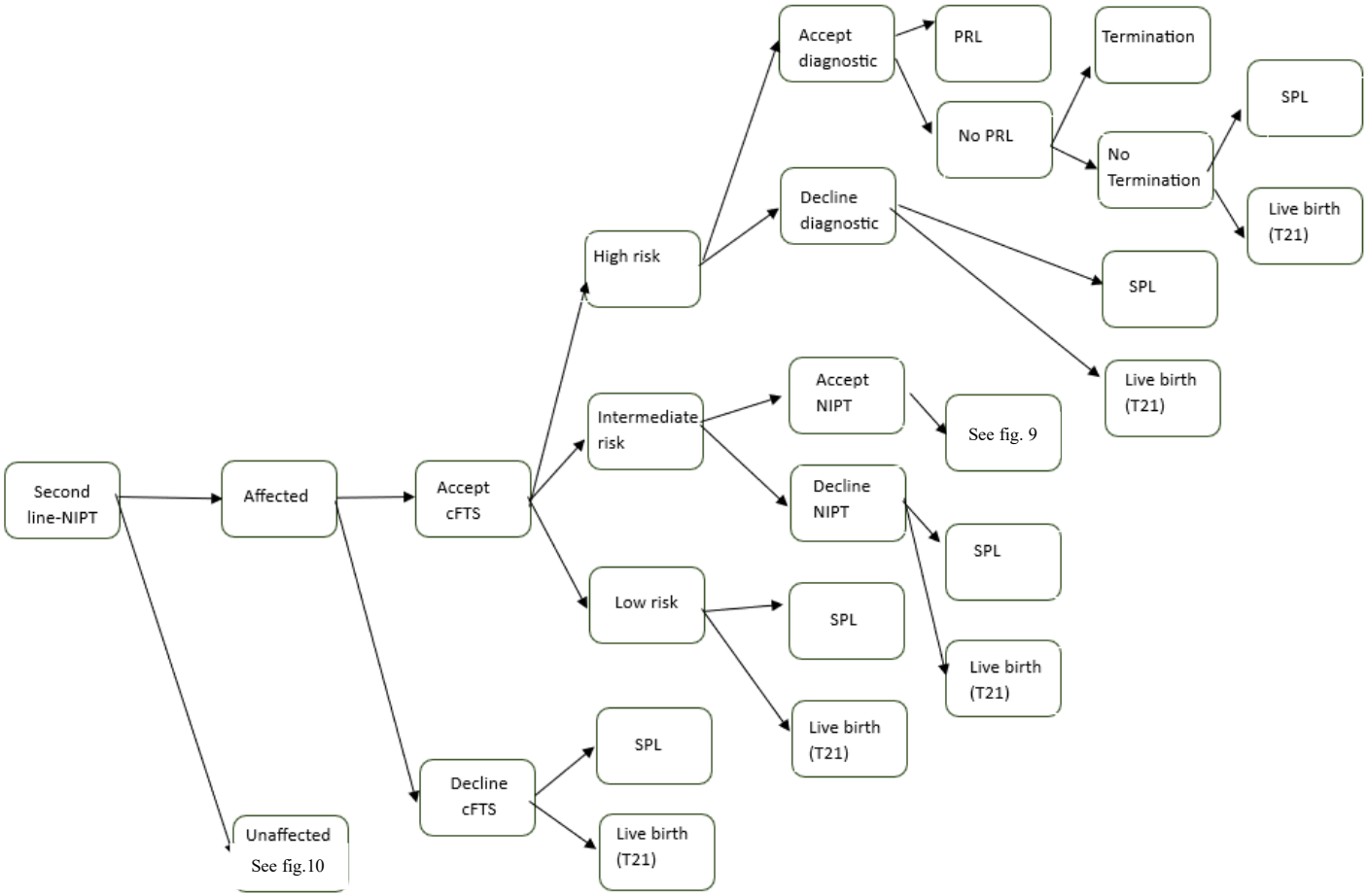


**Figure 8. NIPT affected pathway (all health states included)**

Abbreviations: cFTS, combined first trimester screening; +ve, positive; NIPT, non-invasive prenatal testing; PRL, procedure-related loss; SPL, spontaneous loss; T21, trisomy 21; -ve, negative.


**Figure 9. Accept NIPT (affected, all health states included)**

Abbreviations: cFTS, combined first trimester screening; +ve, positive; NIPT, non-invasive prenatal testing; PRL, procedure-related loss; SPL, spontaneous loss; T21, trisomy 21; -ve, negative.

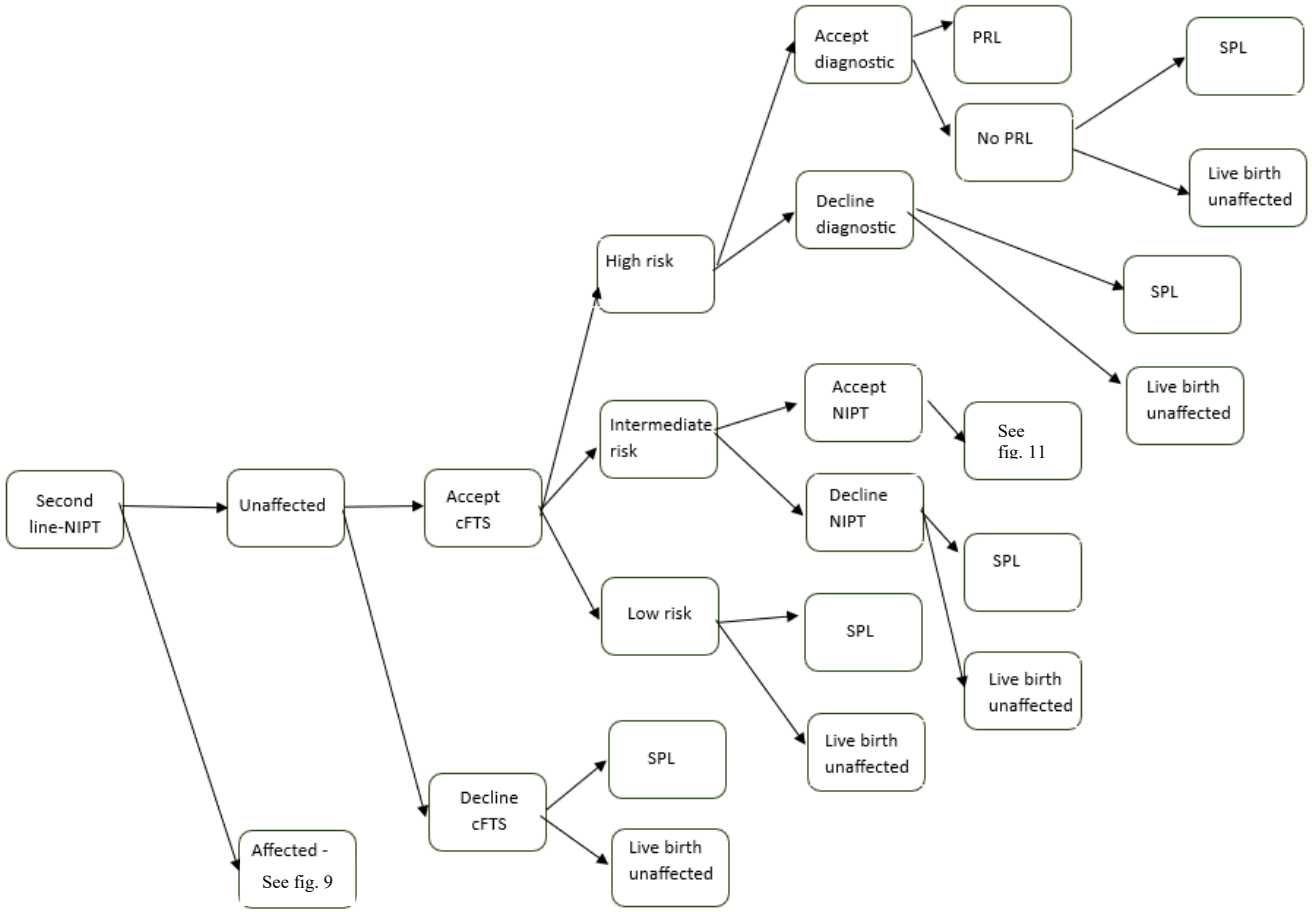


**Figure 10. NIPT unaffected pathway (all health states included)**

Abbreviations: cFTS, combined first trimester screening; +ve, positive; NIPT, non-invasive prenatal testing; PRL, procedure-related loss; SPL, spontaneous loss; T21, trisomy 21; -ve, negative.

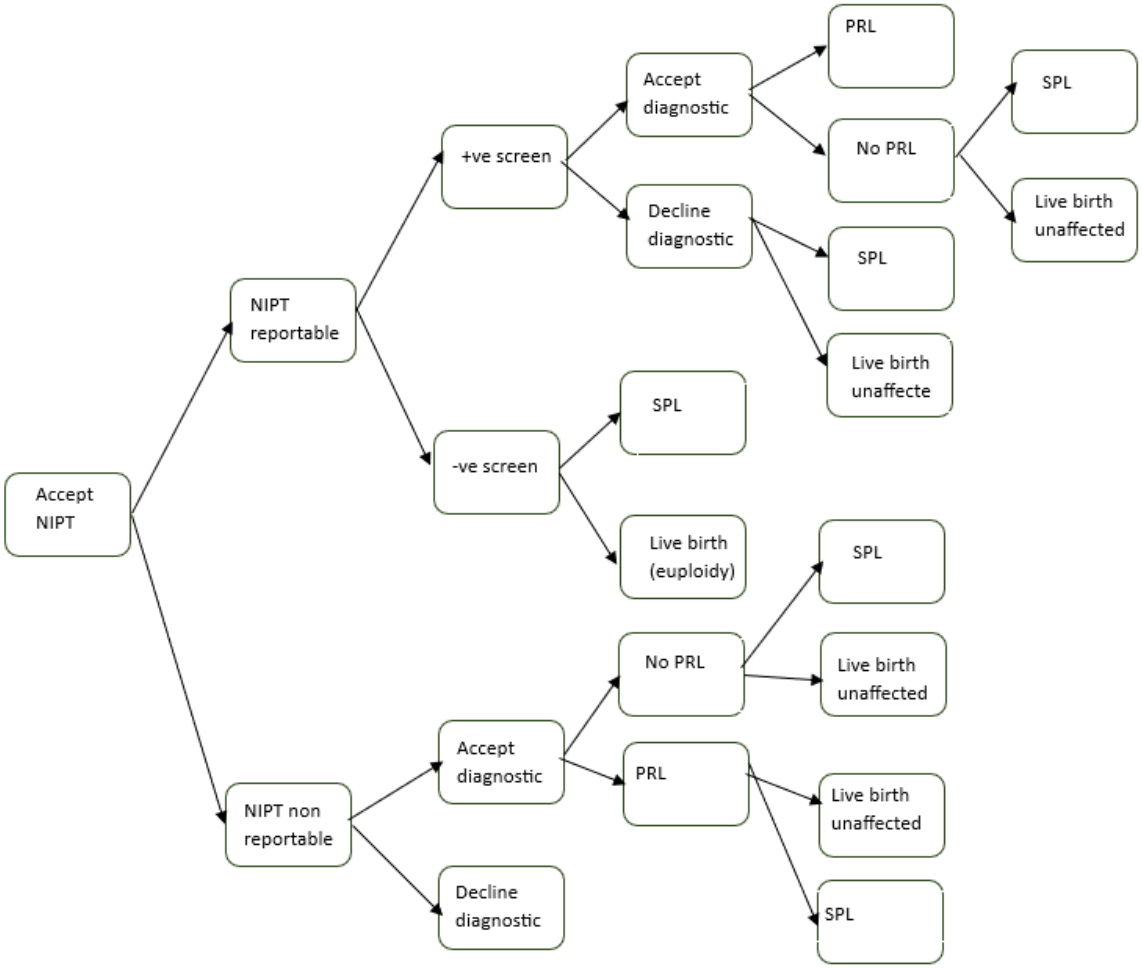


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**Figure 11. Accept NIPT (unaffected, all health states included)**

Abbreviations: cFTS, combined first trimester screening; +ve, positive; NIPT, non-invasive prenatal testing; PRL, procedure-related loss; SPL, spontaneous loss; T21, trisomy 21; -ve, negative.

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# Chapter 4:

# Public perspectives around prenatal screening of chromosomal abnormalities: A focus group study comparing metropolitan and rural/regional areas in Australia.

This chapter presents a thematic analysis of Australian perspectives on prenatal screening. Three focus groups were conducted across the state of New South Wales, in both metropolitan and rural/regional areas. The review in Chapter 2 revealed that economic evaluations often overlook process and intermediate outcomes, primarily due to the scarcity of data on the value associated with these outcomes. This focus group study served as an initial step towards understanding these values and also how they may differ by remoteness.

The primary purpose of the research presented in this chapter was to identify attributes for inclusion in the DCE described in chapter 5, which responded to key challenge 2: Selection of Outcomes. However, it also generated unique insights into the Australian public's views on prenatal screening. The work revealed differences between metropolitan and rural/regional communities, with those in rural areas expressing greater concerns about screening access, including cost, wait times, and distance. The study was published as:

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# Public Perspectives Around Prenatal Screening of Chromosomal Abnormalities: A Focus Group Study Comparing Metropolitan and Rural/Regional Areas in Australia

Amber Salisbury[1,2] | Hovea Winston[3] | Alexis Johnson[1] | Alison Pearce[2,4] | Kirsten Howard[1] | Sarah Norris[1]

[1]Menzies Centre for Health Policy and Economics, University of Sydney, Camperdown, New South Wales, Australia | [2]The Daffodil Centre, The University of Sydney, a Joint Venture With Cancer Council NSW, Sydney, New South Wales, Australia | [3]University of Sydney Medical School, Dubbo, New South Wales, Australia | [4]Sydney School of Public Health, The University of Sydney, Sydney, New South Wales, Australia

**Correspondence:** Amber Salisbury (amber.salisbury@sydney.edu.au)

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## ABSTRACT

**Background:** The widespread and rapid adoption of private payments for non-invasive prenatal testing (NIPT) in Australia has introduced complexities to the decision-making process for the public regarding prenatal screening. NIPT has the potential to be a useful screening tool, but concerns have been raised about its cost, the psychological consequences of testing and the information available to support informed decision-making.

**Objective:** To explore the attitudes, values and beliefs around prenatal screening in Australia, and how perspectives may differ between people living in metropolitan locations versus rural/regional locations.

**Materials and Methods:** Three focus groups were conducted in New South Wales (NSW), Australia. Participants ($N = 25$) were recruited by a market research group. Focus groups took place face-to-face in metropolitan and rural/regional areas, and online via videoconference. Discussions were transcribed and analysed thematically.

**Results:** Participants generally expressed interest in undertaking prenatal screening but held misconceptions about the purpose of NIPT (i.e. screening, not diagnosis) and the conditions assessed. There were varied opinions among participants on expanding the scope of screening: some felt additional information provided reassurance, whilst others thought it would increase stress due to the decreased accuracy. People living in rural/regional areas had greater concerns over access to screening (cost, wait times and distance) than people living in metropolitan areas.

**Conclusion:** Our findings demonstrate different approaches are needed to improve understanding of NIPT (to ensure informed consent), and to improve access to NIPT for people living in rural/regional areas. The pre-test information needs to account for the range of perspectives observed across geographic locations.

The work was conducted at the Menzies Centre for Health Policy and Economics, University of Sydney.

## 1 | Introduction

Prenatal screening is a routine part of pregnancy care in most countries [1, 2]. Traditionally, combined first-trimester screening (cFTS) has been used to offer probability-based information on the three trisomies (T21, Down syndrome; T18, Edwards syndrome; T13, Patau syndrome) in the fetus. This approach involves ultrasound measurements of fetal nuchal translucency (NT), and the evaluation of maternal serum biochemical markers, including ß-hCG and PAPP-A. More recently, non-invasive prenatal testing (NIPT) has been introduced. NIPT uses cell-free DNA (from the fetus) to circulate in maternal plasma. NIPT has a higher detection rate and lower false positive rate for the common trisomies compared to cFTS [3]. In addition, expanded NIPT can detect a broader range of conditions, including microdeletions and duplications, and sex chromosome conditions, although with lower accuracy than when used for the three trisomies [4, 5].

There has been a widespread and rapid adoption of NIPT internationally, using different funding mechanisms [2]. Several countries have incorporated NIPT into their publicly funded national screening programs, including Belgium, Netherlands, Denmark and the UK [2, 6]. In the United States, it is covered by state or private health insurance schemes. In Australia, cFTS is publicly subsidised but NIPT is not. An Australian government consideration in 2019 accepted that a model of the universal offer of NIPT (for trisomies 21, 18 and 13) as a first-line test was clinically efficacious and superior to cFTS, but it was not cost-effective compared to cFTS [7]. It was acknowledged that determining the clinical and economic impact of including NIPT on the Medicare Benefits Schedule (MBS; a listing of the health services subsidised by the Australian government) was difficult and was likely to be influenced by the local availability of biochemical testing and first-trimester ultrasounds (for cFTS), especially in rural and regional areas of the country. This led the government advisory committee to consider the possibility of an MBS item for NIPT which is "limited geographically to women in rural and remote areas".

Numerous studies have explored the complexities and ethical issues raised by the introduction of NIPT. A recent systematic review found an overall desire among pregnant people for increased access to NIPT, although concerns were raised about the financial cost of the test, anxiety surrounding the testing process and the importance of informed decision-making [8]. In Australia, surveys involving women who have undergone NIPT have generally reported positive experiences, but the majority of these women were of high socioeconomic status (SES) and lived in metropolitan areas [9, 10]. Whilst clinicians view NIPT as a useful and high-quality screening test for the common trisomies, they have concerns about how NIPT has been introduced here [11, 12]. Further qualitative research is needed to understand the views of the Australian public, which are known to differ to clinician views [13].

This study uses qualitative methods to gain an in-depth understanding of the attitudes, values and beliefs of Australian adults around prenatal screening. This is the first study to explore whether perspectives around prenatal screening differ between people living in metropolitan locations versus rural or regional locations.

## 2 | Materials and Methods

### 2.1 | Study Design

This qualitative study involved focus groups with adults of childbearing age interested in pregnancy. Focus groups were chosen as they enable the exploration of a variety of different perspectives and experiences through dynamic discussion that allows participants to share and compare their views with others [14]. The study was approved by the University of Sydney Human Research Ethics Committee [2023/170].

### 2.2 | Setting and Participants

Three focus groups with a total of 25 participants were conducted in various geographic locations across NSW. Focus groups were conducted in the following locations (FG1) central Sydney ($n = 9$); (FG2) Dubbo (approximately 400 km Northwest of Sydney) ($n = 6$); (FG3) Online via videoconference ($n = 10$), recruiting participants from rural/regional areas in NSW. FG1 will be referred to as metropolitan, and FG2 and FG3 will be referred to as rural.

#### 2.2.1 | Inclusion and Exclusion Criteria

The inclusion criteria were as follows:

A. Adults (aged 18–45 years old) based in Australia, who have been pregnant in the last 4 years or are interested in becoming pregnant, or

B. Partners of adults who would meet the definition of group A, but whose actual partner may or may not be a participant in the study.

Participants were not able to participate if they could not speak English.

The criteria were developed in consultation with an expert advisory group, which included three obstetricians, a genetic counsellor, a midwife, an ethics researcher working in prenatal screening and a person with a lived experience of NIPT.

### 2.3 | Participant Recruitment

A market research group, Taverner Research, recruited participants using quotas to ensure variation across age, gender and education. Information about rurality, English as a second language and experience with prenatal screening were also captured.

Taverner Research sent potential participants an invitation pack, containing an invitation letter, participant information sheet and consent form. All participants provided consent prior to participation and were compensated for their time with an AU$75 gift card.

## 2.4 | Conducting the Focus Groups and Discussion Content

A rapid literature review was performed to understand the broad scope of features which might impact on views around prenatal screening. Details and results can be found within the Supporting Information. Consultation with the expert advisory group was used to identify priority features for discussion within focus groups (see Table 1).

Focus groups were facilitated by three members of the research team (AS, AJ, HW). One researcher (AS) moderated each focus group according to the discussion guide (see Supporting Information) and a second researcher (AJ or HW) took notes. The discussion guide contained the following: background, warm-up questions and discussion based on the priority features (noting participants were given the opportunity to raise additional features). The scope of conditions was presented to participants as follows:

- The three common trisomies (Down syndrome, Edwards syndrome, Patau syndrome)
- Sex chromosome conditions (using Turner's syndrome as an example)
- Other rare conditions

Participants were presented with two possible options:

- A test that includes the three common trisomies
- A test that includes the three common trisomies, sex chromosome conditions and other rare conditions (referred to as expanded NIPT)

The PowerPoint slides presented to participants prior to beginning the focus group discussions can be found in the Supporting Information. This content was created in collaboration with and approved by the expert advisory group.

## 2.5 | Data Capture, Coding and Analysis of Qualitative Data

Focus groups were audio recorded, transcribed verbatim by a member of the research team (AS) and analysed thematically using QSR NVivo10 qualitative data management software. Two researchers (AS, HW) independently coded the transcripts taking a mixed deductive/inductive approach [15–17]. The transcript data were coded according to broad top-level categories that matched the discussion guide. We then searched for patterns and ideas within the top-level categories and further coded the data into themes and sub-themes, which were developed inductively. Agreement between coders was high and discrepancies were discussed until a consensus was reached (AS, HW). Themes were categorised into the following: attitudes (evaluative judgements individuals hold about various features of testing), beliefs (representations of knowledge that individuals accept as true or hold to be the case) and values (represent what individuals consider important or desirable in life) [18].

# 3 | Results

## 3.1 | Participants

Twenty-five participants were recruited, with their characteristics shown in Table 2.

**TABLE 1** | Features of prenatal screening that were discussed within focus groups.

| Priority features |
|---|
| **Features of the test and test results** |
| What the test covers (common trisomies, sex chromosome conditions, other rare conditions, sex) |
| Number of individuals correctly diagnosed |
| False positive results |
| False negative results |
| Inconclusive results |
| Maternal incidental findings |
| **Features of the process of being screened** |
| Cost |
| Wait time |
| Travel distance to appointments |
| Who provides the information before the test |
| How the results are delivered |
| Who delivers the result |

## 3.2 | Themes

Six themes emerged from the focus groups. Three themes were categorised under attitudes: (1) Access to Health Care Providers and Services; (2) Delivery of information and results; and (3) Pros and cons of expanded NIPT. Two themes were categorised under beliefs: (4) Misunderstanding and lack of awareness and (5) Views of disability. One theme was categorised under values: (6) Value of NIPT. Selected themes and sub-themes are described in more detail below, with additional sub-themes and quotations in Table 3.

## 3.3 | Attitudes

### 3.3.1 | Access to Health Care Providers and Services

**3.3.1.1 | Variable Impact of Cost as a Barrier.** Metropolitan participants engaged in limited discussion around access, and this discussion was focused on cost. Metropolitan participants did not report cost to be a current barrier, but they recognised it as a potential barrier for others and themselves in the past.

> Metropolitan male For our first one, we had the cFTS because we were young and didn't have that much money. Not that we have much right now, but we've had the Harmony test [one commercially available NIPT test] for last two.

In the rural groups, cost was a significant barrier for most participants. Similar to the metropolitan group, they discussed the impact of age and personal circumstances in relation to the cost of testing.

> Rural female ...so I was really sick, and I hadn't been really working, so cost would be huge for us.

**3.3.1.2 | Wait Time Was a Bigger Concern for Those Likely to Experience Longer Delays.** Metropolitan participants did not consider wait times to be an issue affecting them, whereas it was a very important consideration in the rural groups. Several rural participants felt waiting for a result would cause them anxiety and others said wait times would force them to travel to a major city.

**Rural female:** Cause if I had to wait like a week or 2 weeks [for the results], I think I would go mental with anxiety.

**Rural female:** Imagine if that was 6 weeks

**Rural female:** That would be torture

**3.3.1.3 | Travel to Testing: Rural vs. Metropolitan Challenges.** Both metropolitan and rural participants did not want to travel far to access testing, however the definition of 'far' varied between the groups. Within rural groups, travel to testing was associated with a number of additional costs.

**Metropolitan female:** If it's 30 minutes. Maybe not.

**Rural female:** It's a huge problem for anyone that's not living in a metropolitan area. It's not just $420, it's a few days off work, accommodation, travel costs.

### 3.3.2 | Delivery of Information and Results

**3.3.2.1 | Divergent Opinions on How to Receive Information.** Across both metropolitan and rural groups, opinions varied on how to receive information, with some favouring in person, telehealth, or email. Some of the rural participants expressed greater concerns about wait times. Most of this discussion centred on the process of receiving results.

**Metropolitan male:** I think good news you take anyway (laughs). But bad news you take in person.

**Rural female:** I'd be calling being like I don't care, give me a telehealth appointment. Like, fit me in 5 seconds. Like they've just gotta, they've just gotta

**TABLE 2** | Characteristics of participants.

| Characteristics | *N.* participants (%) |
|---|---|
| **Location** | |
| Metropolitan | 9 (36) |
| Rural/regional | 16 (64) |
| **Gender** | |
| Female | 17 (68) |
| Male | 8 (32) |
| **Age** | |
| 18–25 | 3 (12) |
| 26–30 | 9 (36) |
| 31–35 | 3 (12) |
| 36–40 | 8 (32) |
| 41–45 | 2 (8) |
| **Language** | |
| Speaks only English at home | 16 (64) |
| Speaks English and another language at home | 9 (36) |
| **Education** | |
| High school | 3 (12) |
| Trade/certificate/diploma | 10 (40) |
| Undergraduate degree | 7 (28) |
| Postgraduate degree | 5 (20) |
| **Interest in pregnancy** | |
| Pregnant within the past 4 years (or partner) | 15 (60) |
| Interested in becoming pregnant (or partner) | 17 (68) |

**TABLE 3** | Additional themes and/or quotations identified within focus group transcripts, by geographical location.

| Themes | Illustrative quotes |
|---|---|
| **Attitudes** | |
| *1. Access to health care providers and services* | |
| Variable impact of cost as a barrier | *Metropolitan*<br>FG1, female "[In response to another participant stating they would pay for NIPT] Yeah, I think yes, we can cut down on other things, because the well-being [of the child] is very important."<br>FG1, female "I would pay to test for it all [conditions in expanded NIPT]"<br>*Rural*<br>FG 2, female "And I think when it comes to cost, it really depends on like people's personal circumstances cause I would never have been able to afford a 400 and whatever test like it would, that's that would have been my entire Centrelink for like 4 weeks back then. Obviously now I have a job. A full-time job and I'm in a very different place than I was 12 years ago that... Even like if I thought OK, maybe if we even just look back five years ago, I still wouldn't have been able to afford that, like it's only just now that I'm like, OK, yeah. I'm getting a little bit older, I'm in my 30s now so there's other factors that are now at play and would make it the cost worth it, yeah."<br>FG 2, female "Another part of the cost thing is having to go to the doctors, paying for that doctor's trip, getting the test done, paying for that test, going back to the doctor's, paying for the doctor to tell you what the results are. I know that part really hurts."<br>FG 2, female "Because I feel if I didn't have money, I would just want to do it old school."<br>FG 2, female "What do we do? You know, you think. What do we do? Do we come up with this money to get this?" |
| Wait time was a bigger concern for those likely to experience longer delays | *Metropolitan*<br>FG1, male "OK, so obviously you want to get it as early as possible."<br>FG1, female "I'm still the same decision as in don't really mind because it's such a like a short 11 to 18 weeks anyways, so I'm still the same decision, don't really care."<br>*Rural*<br>FG 2, female "Yeah, I'm just thinking like sometimes it takes a month to get into. So if it was restricted you would have to go to Sydney"<br>FG 2, female "Having weeks between when the doctor is available and when you done the test makes me a bit worried."<br>FG2, female "What if there was that significant gap and sometimes here you can wait three weeks for a GP appointment to open up. So it's like you wouldn't be able to see your doctor. And you've had this test 3 weeks ago, and now all you're doing is having anxiety and panic attacks because you don't have that information. You know, just like, constantly thinking about it" |
| Travel to testing: rural vs. metropolitan challenges | *Rural*<br>FG2 female, "I'm from Wilcannia. That's [travel to testing] a huge problem. So yeah, that would have been a factor."<br>FG2, female 1 "If you are getting flown out with RFDS, they're gonna send you to Adelaide for testing."<br>[Would you go to Adeliade to have the test]<br>FG2, female 1 "In my current position, yes, I can understand how a lot of people would not."<br>FG2, female 2 "Probably not me"<br>FG3, male "[what would worry you] the costs and travel distance appointments, because I live in a regional area, so do my wife and I need to travel? How often in a series of periods of time? So yeah, I think those are my major considerations" |

(Continues)

**TABLE 3** | (Continued)

| Themes | Illustrative quotes |
|---|---|
| *2. Delivery of information and results* | |
| Personal preference determines health professional type | *Metropolitan*<br>FG1, male "I think I would prefer a GP, just because I think they'd be they'd be more personally and might if it's bad news or news you weren't expecting, they might be a bit more, you know, sensitive to your situation."<br>FG1, female "I prefer for the obstetrician. Because he or she is the expert in the field and would be in a better position to provide the information than a GP."<br>Metropolitan female "...there are heaps of people out there, so just get it from everyone."<br>Metropolitan female "I think if the person you're seeing is good and specialised in all that, I'd probably be willing to travel, you know longer, within reason."<br>*Rural*<br>FG3 female "[In response to the above comment] Someone else could just give you the news, like a health nurse or something. Sometimes here you can wait three weeks for a GP appointment to open up."<br>FG2, female "I think so as well for myself, it doesn't matter who delivers the result, even if it comes from a GP or an OBGYN. I'll be doing my own research anyways."<br>FG2, female "As long as they probably know the information and they got the right information, then I would accept the info as long as they're they've got the info right with me."<br>FG2, female "Like they've just gotta, they've just gotta tell you exactly what's on their little piece of paper. Not being a doctor, I have no idea. But like, it's just having someone, even if it's like a health nurse or someone else like, knows and understands the information."<br>FG3, female "I think if you've had prior pregnancies with maybe some concerns, then maybe the generic counsellor might be the way to go. But if everything's kind of sailing along smoothly, then I think that would be a scary extra step if someone suggested to see a genetic counsellor to me anyway."<br>FG3 female "I feel like GP would have been good, because where I am, you don't go to the obstetrician until you're 12 weeks or 13 weeks. So it's like he kind of expected me to already know, because that's when you get the testing done." |
| Lack of trust in health care professionals to be sensitive | *Metropolitan*<br>FG1, male "So like, you know, coming from a bloke's point of view. That, you know, doctors and obstetricians like, they study for a long time, but maybe not in the delicacy of sensitivity. And that poor girl was, like, you know, communicated to poorly. So I think for me, if there is an issue, it should not be negative, not the result, how it's communicated. Yeah. So just some more training around like sensitivity."<br>*Rural*<br>FG2, female "I had to change my doctor because I like I felt a bit more comfortable with another doctor, so I had to look out for like a new doctor."<br>FG2, female "There was one and I was like never coming back to you again. You're in the bin. I don't think he actually did anything wrong but I was like 'nah'. And I don't care, I'll go and see anybody and does not matter who you are, I just want to see someone because I hate doctors and I'm only here for a very specific reason so, but yeah, this one doctor has like bad vibes."<br>FG3, female "So and sometimes and I've experienced this myself. Sometimes it's a bit feels a bit hit or miss with going into GPs, and they just trying to get people in and out, make up time" |

(Continues)

**TABLE 3** | (Continued)

| Themes | Illustrative quotes |
|---|---|
| Divergent opinions on how to receive information | *Metropolitan* |
| | FG1, female "Same same agree, yeah, especially like if I have some question to ask, I can get it sorted over the phone straight away, without like making another appointment, waiting time..." |
| | FG1, female "I think good news you take anyway. But bad news you take in person." |
| | FG1, male "[In response to the question of how they would like to receive results] I'd prefer to go and see in person" |
| | *Rural* |
| | FG3, male "I think I prefer to have it via email, rather than in person. So that I can have time to collect my thoughts and compose myself, and then to really articulate my questions." |
| | FG3, male "I'll prefer yeah, if it is, there is a very long wait time, yeah, I want to get the results over the phone. But I need the follow up within very short time, because face to face I need for the details, discussions." |
| | FG2, female "Maybe they could look at implementing if you've got a low risk you'll hear from us when we're ready, if you're high risk we're going to call you." |
| | FG2, female "Yeah, I think if it was high risk, I would like to be in person because then they'll obviously be questions, discussion about next steps and that kind of stuff, but low risk, I'll take it over the phone, yeah." |
| | FG2 female, "As quick as the information can come to me, I don't care how blunt it is, or how it's given." |
| | [How would you prefer to receive results?]<br>FG3 female, In person, but it was like coupled with another appointment.<br>FG3 male Yeah in person.<br>FG3 male, Yeah. Likewise. |
| *3. Pros and cons of expanded NIPT* | |
| Increasing information paradox: reassurance vs. uncertainty | *Metropolitan* |
| | FG1, male "I think even I agree that testing for everything [expanded NIPT] should be done so we're at least prepared for what's to come." |
| | FG1, female "So I think the false positive thing is kind of like a big concern, and people would probably need like more actual numbers on how accurate the results are. And then also just the stress the patient would be going through, to hear about false positive result" |
| | FG1, male "If you test for everything [expanded NIPT], then you can make an informed decision. How to proceed further and all that kind of stuff" |
| | *Rural* |
| | FG3, male "So I'd rather have small set of endpoints determined, but more accurate as compared to various conditions, but with less accuracy" |
| | FG2, female "[In response to discussion about expanded NIPT] yeah, it might encourage people to choose a test that has more scope, because then you've got a greater chance of picking up things that you might not otherwise have seen in both mother and child." |
| | FG2, female "It [false positives] would be a concern for myself, because we do have family members who have quite a significant disability and I can see how much pressure it puts on my fairly old parents at the moment, and we don't want to go through that" |
| | FG2, female "Any information is good information" |
| | FG3, female "It would impact my decision [on testing for a broader range of conditions]. You want something that is quite accurate really." |

(Continues)

**TABLE 3** | (Continued)

| Themes | Illustrative quotes |
|---|---|
| **Beliefs** | |
| *4. Misunderstanding and lack of awareness* | |
| NIPT misrepresented as a diagnostic tool | *Metropolitan*<br>FG1, male "Is that the harmony test?"<br>*Rural*<br>FG2, female "whoever is advising of these tests needs to really communicate that to you that there is that risk of a false positive or a false negative. I mean that's something that you have to act upon that you. You have to make that informed choice about whether or not you're willing to accept that." |
| Limited understanding of scope of testing | *Rural*<br>FG2, female "What are these [sex chromosome conditions]?" |
| *5. Views of disability* | |
| Challenges of parenting a child with a disability | *Metropolitan*<br>FG1, male "Down syndrome people are amazing and they're beautiful and very lovely. But you know, whether you can have it at that time in your life, maybe there's some people who can't."<br>Rural<br>FG 2, female "It would sting for the majority of people, but also the long-term effects of having child with a disability would also sting and cost a lot more"<br>FG2, female "I was like ohh a baby's a baby, I'm happy, I'm good, it doesn't. matter, whereas now I'm like, OK, there's complexities around costs, what I have to do, all the flow on effects like if there are pretty significant disabilities, then, that would be something that I would factor in"<br>FG2, female "No, no, I think I would just be really, really shocked. Disappointed. Is that a bad word to use? We do have family members who have quite a significant disability and I can see how much pressure it puts on my fairly old parents at the moment, and we don't want to go through that so, based on your story, I would potentially abort a healthy baby with these results." |
| **Values** | |
| *6. Prioritisation of NIPT* | |
| Differing values influencing NIPT decision-making between metropolitan and rural communities | *Metropolitan*<br>FG1, female "[In response to another participant stating they would pay for NIPT] Yeah, I think yes, we can cut down on other things, because the well-being [of the child] is very important."<br>*Rural*<br>FG2 female "I was 22 when I had my first one and I didn't do any screening. I was healthy, I was young, I was fairly confident it was gonna be fine"<br>FG2, female "[response] I agree with you, with that like if you've got genetic histories and you have got some sort of disabilities where it could be diabetes, whatever. Like, if you know one that's in your family history, then yeah, I would agree with you. You know to get all the tests. You know, possibly down, no matter how much it's gonna cost me."<br>FG2, female "[response] Yes, that's the attitude, yeah."<br>FG2, female "Yeah, like, so I'm 12weeks pregnant. So we're just going through the whole process as well. So my husband and I discussed, and we've decided that we would probably do the old method where we do that first line test. Because the cost of an NIPT at the moment is $420.00. So that's still a lot of money for us and you know we're we're both relatively young." |

Abbreviations: FG; focus groups, NIPT; non-invasive prenatal testing.

tell you exactly what's on their little piece of paper.

**Rural female:** As quick as the information can come to me, I don't care how blunt it is, or how it's given.

**3.3.2.2 | Personal Preference Determines Health Professional Type.** Participants from both metropolitan and rural groups had differing views on which healthcare professional should deliver the pre-test information and results. All participants were unaware of genetic counsellors, with some participants making negative assumptions about their role.

**Metropolitan female:** [In response to asking if participants had heard of a genetic counsellor] Before today? No, no I hadn't.

**Metropolitan male:** Genetic specialist. I mean, it sounds like very expensive, but also sounds like they're not you know, trained in other ways

Within the rural groups, the choice of healthcare professional appeared to be driven by cost and wait time.

**Rural female:** It would obviously depend on you know the costs involved with seeing that person, distance to travel, all that sort of thing as well. I highly doubt in a regional area, you're gonna have an enormous supply of those guys [genetic counsellors] hanging around.

### 3.3.3 | Pros and Cons of Expanded NIPT

**3.3.3.1 | Increasing Information Paradox: Reassurance Versus Uncertainty.** Several participants preferred a broader scope of conditions, despite reduced accuracy, as they felt more information provided increased reassurance. Conversely, other participants felt that the decreased accuracy resulted in greater uncertainty. Within the rural group, there was an in-depth discussion about the anxiety that would be caused by the decreased accuracy.

**Metropolitan male:** I think testing for everything is good because even if it's not 100% accurate all of them, it's worth it right? At least it's better to know a little bit more possibility as opposed to not knowing it.

**Rural female:** So is it like a catch 22. Do you want to know more about your child to get those proper positive results or the chances of the negative sides of the testings.

## 3.4 | Beliefs

### 3.4.1 | Misunderstanding and Lack of Awareness

**3.4.1.1 | Misrepresentation of NIPT as a Diagnostic Tool.** Across all focus groups, participants with lived experience (either currently pregnant, or previously pregnant) referred to NIPT as the *'Harmony test'* (a commercial brand of NIPT) and were under the impression it was diagnostic.

**Metropolitan male:** We've had the harmony test for last two. Like if we did have any positive results, it would not have changed us wanting to have the babies, but with the harmony test we've been told it was conclusive.

**Rural female:** I would potentially abort a healthy baby with these [positive screening] results.

**3.4.1.2 | Limited Understanding of Scope of Testing.** Across all focus groups, most participants were only familiar with Down syndrome and did not appear to have knowledge of the other conditions. One participant believed the prenatal screening they underwent was only for Down syndrome, even though it likely included the other two common trisomies.

**Metropolitan male:** From our experience the test was done just for Down syndrome... but the other ones, I've never heard of them, to be honest, and like short height and the ovaries like that [Turner syndrome], to me is not really that bad.

**Rural female:** I think I asked about it and they said you're getting tested for the genetic stuff and I'm guessing they just gave me the basic one.

### 3.4.2 | Views of Disability

**3.4.2.1 | Challenges of Parenting a Child With a Disability.** Participants in both groups expressed acceptance of children with disabilities, whilst acknowledging the belief that raising them presents potential challenges. Within the metropolitan group, participants raised the issue that some people might not feel able to raise a child with a disability, although none of them identified themselves that way. In the rural focus groups, participants discussed the challenges relevant to them.

**Metropolitan male:** We adopted a child because the family couldn't afford it, because they had like three children and got told it's healthy, but it wasn't.

**Rural female:** It's hardest now just to pay rent and groceries. It wouldn't be fair on the child to, you know, bring that child in and knowing that I won't be able to afford the needs, the travel, the appointments to get that child, what that child needs when it arrives.

## 3.5 | Values

### 3.5.1 | Prioritisation of NIPT

**3.5.1.1 | Differing Values Influencing NIPT Decision-Making Between Metropolitan and Rural Communities.** In the metropolitan group, participants valued

choosing NIPT as a way to act in the best interests of their child. On the other hand, rural participants, who faced access barriers, valued NIPT based on their perceived chance of having a child with a chromosome condition. This concept of perceived chance and how it related to the value of NIPT was not raised by metropolitan participants.

**Metropolitan female:** Even I am in favour of testing for as much as possible, because that would be ultimately it's in the interest of the child. So as much as possible, I think testing.

**Rural female:** Now, if I were to have another child. I'm in my late 30s, I'm higher risk, I'll be doing screening and testing.

## 4 | Discussion

These focus group results provide evidence regarding Australian public attitudes, beliefs and values around prenatal screening. Both metropolitan and rural groups exhibited similarities, including a desire to undergo prenatal screening and misconceptions around the screening tests available and the conditions assessed. The desire to undertake screening occurred within a social context where participants demonstrated acceptance towards individuals with disabilities whilst acknowledging potential challenges of raising a child with a disability. Our findings suggest there are differences in attitudes between people living in metropolitan versus rural locations, particularly with respect to the different elements of access to screening (cost, wait times and distance).

Metropolitan and rural participants differed in their attitudes towards access. The cost of NIPT was a major barrier for rural participants, whilst metropolitan participants did not perceive this to be an issue given their financial circumstances. Concerns over inequities of access due to the relatively high cost of NIPT between families with high and low SES have been described internationally [8, 19] and in Australia [11]. This is in line with the results of this study, as rural families generally have lower SES [20]. This study adds to the literature by identifying additional inequities related to geographical location. In contrast to metropolitan participants, rural participants expressed concerns about wait times for accessing GP appointments, ultrasounds and follow up testing, as well as the need to travel to access these services. Additional costs associated with travel were raised by rural participants, including the cost of transport, accommodation and loss of income. International qualitative studies have found wait times to be a common concern but differences by geographic location have not been explored [8, 21, 22]. Discussions are limited within the literature regarding the distance travelled to access prenatal screening. This study highlights the multifaceted inequities faced by rural communities in accessing prenatal screening services.

The current study finds divided views on expanding the scope of conditions included in prenatal screening, with no clear differences between metropolitan and rural groups. Two models of thought became apparent, one in which additional information offered reassurance, and another where it heightened uncertainty and stress, consistent with focus groups conducted in Canada [8]. In Australia, clinicians are worried about the psychosocial harms and ethical concerns resulting from expanded NIPT, especially when screening for sex chromosome conditions and microdeletion and microduplication syndromes [11, 12]. These screenings are linked to high rates of false positives and variable phenotypes, which can further complicate the interpretation of the results. Our findings indicate that whilst several participants supported broadening the scope of testing, many lacked understanding regarding the conditions that can be screened. This contrasts to previous Australian studies, where people who have undergone NIPT have generally reported being satisfied with pre-test information [9, 23]. This raises questions about whether pregnant couples are truly providing informed consent and making informed decisions. Traditionally, consent discussions have focused on procedural risks, rather than the potential outcomes of the test, as observed with invasive prenatal diagnostic procedures. However, with NIPT, the minimal procedure-related risk removes this traditional barrier and contributes to its routinisation. It has been suggested that the routinisation of testing shortens the decision-making process, creates an expectation for pregnant people to undergo testing and minimises the perceived importance of these decisions [24]. Similar concerns have been raised in health systems that publicly fund NIPT, where it is perceived as a routine test with no cost, meaning there is no friction causing people to think about the gravity of their decision and possible implications [8].

The current study indicates the Australian public may not prioritise the method by which they receive information, even in the face of existing challenges related to information access. This observation was seen across the type of healthcare professional and mode of communication, during the delivery of pre-test information and test results. Contrary to expectations, there were mixed attitudes towards genetic counsellors, with a lack of awareness and some negative assumptions about the profession. This is consistent with an international quantitative study on preferences for prenatal diagnosis, which found women were indifferent between receiving results from a genetics specialist or non-specialist [25]. It is important to note that clinicians and policymakers view genetic counsellors as capable of providing higher quality support, and in Australia, they are recommended for individuals receiving high-chance results [26]. Our study reveals varied opinions on the preferred mode of receiving information. These findings align with a recent international quantitative online survey, which found women preferred information to either be text-based, in person, or through an app, but not in a group discussion [27]. Interestingly, recent Australian evidence within a socioeconomically disadvantaged population found different forms of counselling for prenatal screening did not have significant differences in effectiveness [28]. An additional finding from our study was participants with lived experience of NIPT believed it to be a diagnostic test, and those who were pregnant found it challenging to obtain information.

The introduction of NIPT may have implications for people living in rural locations in accessing prenatal screening. Whilst the cost of NIPT may be a challenge for these communities, NIPT could actually mitigate the need for extensive travel as only a blood test is required (whilst cFTS requires an ultrasound), and there are fewer unnecessary diagnostic tests [3]. This supports

the argument for public funding for NIPT based on geographic location. To improve understanding of the test and test results, there should be a focus on (1) the information provided by the test and (2) information dissemination. First, ensuring the test information itself is improved, for example, by excluding conditions with very low positive predictive values. Second, ensuring clear information is widely available. Since the type of healthcare provider does not appear to be important, alternative providers such as practice nurses could be trained to provide this information. Although this would require significant investment, it would act as a protective buffer against misconceptions around prenatal screening. By employing these strategies, genetic counsellors could then be prioritised for those who receive high-chance results, whilst addressing potential negative attitudes towards the profession. The use of digital technologies could also be explored to improve access in rural areas.

### 4.1 | Limitations

This research explores patterns and overall views of members of the general population from NSW but does not represent every individual in metropolitan and rural/regional areas across Australia. For instance, the cost of NIPT is likely to be a barrier for some pregnant people and partners in metropolitan locations, and people living in remote or very remote areas in Australia may have different views. Although we aimed to explore the views of females and males, most participants were female. The sample size was deemed sufficient to identify key themes and provide illustrative examples. However, a larger sample size could have facilitated a deeper understanding of these themes and ensured data saturation. As part of the information collection prior to the focus groups, we included questions on lived experience. However, this question was not completed by many participants; instead, it emerged organically during the discussions. We excluded people who could not speak English, who are likely to experience additional barriers in accessing prenatal screening and who are also likely to be members of culturally and linguistically diverse communities who in turn are likely to have different perspectives to the study participants.

## 5 | Conclusion

In the absence of public funding and a nationally coordinated approach to the implementation of NIPT in Australia, we have identified concerns regarding inequities in access to NIPT, the extent to which pregnant people and their partners understand the purpose of NIPT (i.e. screening, not diagnosis), and the implications of these for parental decision-making in the antenatal period arising especially in the context of tests with different scope (i.e. three common trisomies only versus expanded testing for other conditions). Our findings highlight that different policy approaches are needed to improve access to NIPT for people living in rural areas, to ensure informed consent for NIPT, and that the pre-test information provided to pregnant people and their partners clearly accounts for the range of public perspectives observed across different geographic locations.


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#### Conflicts of Interest

The authors declare no conflicts of interest.

#### Data Availability Statement

The data used in this study is accessible upon reasonable request from the corresponding author, in accordance with the confidentiality agreements and ethical considerations governing the research. Requests for access to the data should be directed to Amber Salisbury at amber.salisbury@sydney.edu.au.

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## Supporting Information

Additional supporting information can be found online in the Supporting Information section.

# Supplementary materials

## Section A. Rapid literature review

A rapid literature review was performed in the University of Sydney library to understand the broad scope of factors that may influence preferences during prenatal screening. The search was limited to systematic reviews and used search terms similar to the following: "prenatal testing", "non-invasive prenatal testing", and "preferences". It revealed a recent (2021) systematic review of quantitative and mixed-methods studies of factors that affect decision-making processes during prenatal testing.[1]

The systematic review included 46 studies in its qualitative synthesis. A member of the research team (AS) collated and compared the factors within the included studies. Fifty-four factors were identified and classified into the following groups: (1) outcomes; (2) personal; (3) process; (4) psychosocial; and (5) test (**Table 31)**

**Table 31. Factors that may influence parental decision making in prenatal testing**

| Factor type | Factor |
|---|---|
| Outcomes | False negative cases |
| | False positive cases |
| | Fertility treatment |
| | Quality of life |
| | Social impact |
| | Uncertain results |
| Personal | Acceptability of having a baby with DS |
| | Accurate recall of risk estimates |
| | Clinical characteristics |
| | Family history |
| | History of spontaneous miscarriage |
| | Intention to participate in screening |
| | Knowledge of Down syndrome |
| | Knowledge of screening tests |
| | Knowledge of invasive testing |
| | Knowledge of intentions of outcome of pregnancy based on test results |
| | Maternal age |
| | Perceived risk of having a baby with DS |
| | Perceived risk of PRL |
| | Personality |
| | Previous child with illness |

| | |
|---|---|
| | Relational factors |
| | Risk taking |
| | Sociodemographic characteristics |
| | Understanding of screening results |
| | Values, beliefs and attitudes |
| Process | Available public funding |
| | Convenience of procedure |
| | Cost |
| | Decision making process |
| | Impression of clinician's preference |
| | Information provision |
| | Method of receiving results |
| | Method of risk reporting |
| | Satisfaction with decision making process |
| | Test location |
| | Time to make a decision |
| | Timing of genetic counselling |
| | Type of healthcare provider delivering results |
| | Wait time for results |
| Psychosocial | Anxiety |
| | Decisional conflict |
| | Decisional regret |
| | Depression |
| | Perceived choice control |
| | Personal wellbeing |
| | Pregnancy stress |
| | Psychosocial factors |
| | Regret |
| | Worries in pregnancy |
| Test | Miscarriage risk |
| | Sensitivity |
| | Specificity |

Abbreviations: DS, Down syndrome; PRL, procedure-related loss

## Section B. Discussion guide

**Table 32. Discussion guide**

| Section | Description | Key questions | Prompts |
|---|---|---|---|
| Warm up1 – ice breaker | Warming up the participants by getting them to introduce themselves and establishing a relaxed environment | Can everyone please introduce themselves | What is your name and what do you spend most your time doing? |
| Section 1 | Discuss each feature on the list, with reference to the levels, and to the wording of features and levels | What does [feature/level] mean to you?<br>What wording would make the features or levels easier to understand?<br>Which of these are important to you and why?<br>Which features do not seem important to you and why? | How would feature X influence your decision to take part in the screening program? |
| Section 2 | Groups will be asked to discuss the ranking of features and then to individually rank the features after the discussion using an online form. | How would you order the features from most to least important? | Which feature ranking do you not agree with?<br>Which feature do you think is most important?<br>Which feature do you think is least important? |
| Final question | Last question to gather any extra information | What are your final thoughts on the on the different ways of ranking the features?<br>How were people's opinions changed through the discussion?<br>Is there anything else you would like to add to this discussion? | What changed your mind? |

## Section C. Supplementary material references

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# Chapter 5:

# Australian preferences for prenatal screening: A discrete choice experiment comparing metropolitan and rural/regional areas

This chapter presents a DCE exploring preferences for prenatal screening, with a focus on differences between metropolitan and rural/regional areas of Australia. The attributes included within the DCE were derived from the findings of the qualitative focus groups described in the previous chapter and expert advice. This study quantified the value of prenatal screening features, including the following two intermediate outcomes: the psychological impacts of (1) inconclusive results and (2) false positive results. WTP estimates were calculated for these outcomes so that they could be incorporated into two of the demonstration models presented in Chapter 3.

The primary purpose of this study was to quantify intermediate outcomes for use in economic models, thereby responding to key challenge 2: Selection of Outcomes. However, the study also highlighted the importance of healthcare professionals considering differing preferences between rural and metropolitan populations when delivering prenatal screening. This study was published as:

> **Salisbury A,** Norris S, Pearce A, Howard K. Australian preferences for prenatal screening: A discrete choice experiment comparing metropolitan and rural/regional areas. *Applied Health Economics and Health Policy*. 2025; 1-14.

Applied Health Economics and Health Policy
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ORIGINAL RESEARCH ARTICLE

# Australian Preferences for Prenatal Screening: A Discrete Choice Experiment Comparing Metropolitan and Rural/Regional Areas

**Amber Salisbury**[1,2] · **Sarah Norris**[1] · **Alison Pearce**[2,3] · **Kirsten Howard**[1]

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## Abstract

**Background** Non-invasive prenatal testing has the potential to be a useful genetic screening tool in Australia. However, concerns have been raised about its cost, commercial provision, the psychological impacts of the screening process, and disparities in access experienced by rural and regional communities.

**Aims** The aims of this study are (1) to estimate Australian preferences for features of prenatal screening; (2) to explore potential variations in preferences between metropolitan and rural/regional communities; (3) to estimate the extent to which respondents are willing to trade-off between attributes, using willingness to pay (WTP) and willingness to wait estimates.

**Methods** A discrete choice experiment (DCE) was conducted with 12 choice tasks. The DCE recruited participants from metropolitan ($n = 160$) and rural/regional ($n = 168$) locations across Australia. Mixed logit and latent class analyses were conducted and WTP and willingness to wait were calculated.

**Results** Both metropolitan and rural/regional preferences were significantly impacted by the false-positive rate, false-negative rate, and cost. In addition, rural preferences were significantly impacted by the scope of the conditions covered, the inconclusive rate, and wait times. The number of screening tests and revealing the sex of the foetus were not significant within either group. Willingness to pay estimates ranged from AU$13 to avoid a test with a 1% increase in the false-positive rate to AU$323 to screen for a wide range of conditions.

**Conclusions** This study highlights the importance of considering differing preferences between rural and metropolitan populations when delivering prenatal screening. Further, this study provides Australian-specific WTP estimates to be incorporated into economic evaluations.

## 1 Introduction

Recent advancements in technology have led to the introduction of non-invasive prenatal testing (NIPT). Non-invasive prenatal testing uses cell-free DNA (also referred to as cell-free DNA screening) [1], circulating in maternal plasma to detect chromosomal abnormalities in the foetus [2]. Non-invasive prenatal testing offers a higher detection

**Key points for decision makers**

Non-invasive prenatal testing (NIPT) could be a valuable genetic screening tool in Australia. However, concerns exist about its cost, commercial provision, psychological impacts, and access disparities in rural areas.

This study found that while metropolitan preferences were shaped by the accuracy and cost of screening tests, rural preferences were influenced by a broader range of screening features.

This study provides Australian-specific WTP estimates to be incorporated into economic evaluations, which could directly inform future decisions around NIPT that explicitly account for Australian preferences.

✉ Amber Salisbury
amber.salisbury@sydney.edu.au

1 Menzies Centre for Health Policy and Economics, Sydney School of Public Health, University of Sydney, Sydney, NSW, Australia

2 The Daffodil Centre, University of Sydney, A Joint Venture with Cancer Council NSW, Sydney, NSW, Australia

3 Sydney School of Public Health, University of Sydney, Sydney, NSW, Australia

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rate and lower false-positive rate for the three common trisomies (T21, Down syndrome; T18, Edwards syndrome; T13, Patau syndrome) compared to traditional combined first-trimester screening (cFTS), which involves an ultrasound and maternal serum biochemical marker evaluation of beta human gonadotropin and pregnancy associated plasma protein A. Non-invasive prenatal testing offers additional advantages, such as the capability of detecting a broader range of conditions, including microdeletions and duplications and sex chromosome conditions (e.g., Turner syndrome and Klinefelter syndrome), as well as revealing the sex of the foetus [3, 4]. However, NIPT is associated with a higher cost compared to cFTS, displays decreased accuracy when applied to the broader range of conditions, and these conditions present with variable phenotypes. There are two approaches for using NIPT: a first-line test offered to all pregnant women; or a second-line test offered only if there is a high-risk result on cFTS. In Australia, cFTS receives a public subsidy, whereas NIPT predominantly does not. Non-invasive prenatal testing is gaining popularity, and this is raising equity concerns given the lack of public funding and absence of a formal implementation plan [5, 6].

Applications to the Australian government seeking public subsidy for NIPT have been unsuccessful. Although the Australian government accepted that NIPT (for trisomies 21, 18 and 13) was clinically efficacious and superior to cFTS, it was not considered to be cost effective compared to cFTS (at an estimated AU$510,769 per extra trisomy detected [7]. The consideration highlighted the challenges in assessing the economic impact of including NIPT on the Medicare Benefits Schedule (MBS; a listing of the health services subsidised by the Australian Government). These challenges included accounting for the psychological consequences of the screening process and addressing disparities in rural and regional areas with limited access to ultrasounds (an essential component of cFTS) and follow-up invasive testing. Indeed, the government advisory committee noted that a geographically restricted MBS item, targeting rural and regional areas, might be an approach for future consideration. Recent guidelines from the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) advocate for research to explore preferences for prenatal screening, particularly in rural and regional areas [8]. This research will assist in developing a formal and equitable implementation model for prenatal screening in Australia.

Much has been written about preferences for prenatal screening overseas. A recent systematic review identified 46 quantitative and mixed-method studies and highlighted the complex decision-making processes involved in prenatal screening. Decision-making factors extended far beyond the diagnostic rate, to include procedural aspects (e.g., information provision, convenience and wait time for results) and the psychological impacts of receiving false or uncertain results, which can be exacerbated by longer wait times. Despite the large number of studies identified, none were conducted in Australia, where preferences have been shown to differ in the context of prenatal diagnostic testing [9]. Preferences of the Australian public for cFTS have been assessed prior to the introduction of NIPT [10], and there have been studies on the preferences of pregnant women undergoing NIPT [11, 12], as well as a recent investigation into preferences specific to Western Australia (WA) [13]. However, there remains a gap in the evidence around Australian-wide preferences for prenatal screening in a context where NIPT is locally available.

To explore Australian preferences for prenatal screening, we have used a discrete choice experiment (DCE). Discrete choice experiments are stated preference methods used to understand the trade-offs people make between programme features (known as attributes) [14]. This study aims to (1) explore Australian preferences for features of prenatal screening; (2) explore potential variations in preferences between metropolitan and rural/regional communities; (3) estimate the extent to which respondents were willing to trade-off between attributes, including willingness to pay (WTP) estimates, which could be used in future economic evaluations.

## 2 Methods

### 2.1 Study Design

Preferences for prenatal screening were elicited using a DCE, designed and developed according to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Conjoint Analysis Task Force for good research practices checklist [15]. This DCE presented participants with a series of questions, asking them to choose between three scenarios: two unlabelled alternative approaches to prenatal screening, or 'no screening'. Each alternative included attributes (i.e., features of the programme such as the cost and false-positive rate) with varying levels. By administering multiple choice tasks to each participant, we were able to quantify the relative importance of attributes and their levels. By including cost as one of the attributes, we were able to calculate the WTP for particular attributes of the programme. Calculating WTP provides an avenue to integrate intermediate (i.e., the impacts of receiving false or uncertain results) and process outcomes into economic evaluations and applications for public funding [16].

## 2.2 Setting and Participants

The DCE was conducted as a web-based survey through Qualtrics. Discrete choice experiment participants included: (A) adults (aged 18 to 45 years) based in Australia, who have been pregnant or are potentially interested in becoming pregnant, or (B) partners of adults who would meet the definition of group A, whose actual partner may or may not be a participant in the study. People who could not speak English were excluded from the study. The DCE population will be referred to as the 'general public with an interest in pregnancy'.

This population was chosen was to ensure the survey was presented only to those for whom it is relevant and enhances the relevance of the DCE choice tasks for respondents. In contrast to the majority of previous studies which focus on women [17], all genders were included in this study to recognise the role partners play in the decision-making processes [18, 19].

Participants were recruited through an independent external web-panel provider (Dynata). Participants were recruited from the panel provider's existing online research panel and were emailed a link to the survey from the panel provider. Quota sampling was used to ensure diversity across gender and geographical location, ensuring we had at least 50% of the sample recruited from non-metropolitan (i.e., inner regional, outer regional or remote) areas across Australia. Data were collected between February 15th and April 5th, 2024. The study was approved by the University of Sydney Human Research Ethics Committee [2023/170].

## 2.3 Attributes and Levels

The DCE attributes and levels were informed by a review of the literature, consultation with an expert advisory group (EAG) and a series of focus group discussions. A rapid literature review was performed to understand the broad scope of attributes that might impact on preferences for prenatal screening. Details and results can be found within the Supplementary materials. Consultation with the EAG was used to identify priority attributes for discussion within the focus groups. The EAG included a diverse group of relevant healthcare professionals currently working in Australia, including four obstetricians, a genetic counsellor and a midwife, as well as an ethics researcher specialising in prenatal screening, and a person with lived experience of NIPT who received a false-positive result. The priority attributes chosen for focus group discussion can be found within the Supplementary materials.

Three focus groups were set up in New South Wales, Australia. The focus groups comprised 25 participants of childbearing age from the general public with an interest in pregnancy. Focus groups took place face-to-face in metropolitan and rural/regional areas, and online via videoconference recruiting from rural/regional areas. Discussions were transcribed and analysed thematically using NVIVO qualitative software. An extensive description of the focus group methodology is provided elsewhere [20] . Focus group results were discussed with the EAG to determine the final attributes and levels for inclusion within the DCE. The eight attributes included within the DCE can be found in Table 1. The EAG provided valuable input on the wording of attributes and levels to ensure participant understanding, e.g., 'chance of a missed case' and 'chance of a false alarm' representing false negatives and false positives. Attributes which involved risk estimates were presented using two formats: numerical (expressed as the number of babies or tests out of 100) and visual (using an icon array, consisting of a matrix of 10×10 squares with colours representing proportions).

The selected levels were based on the literature, focus group discussions, and consultations with the EAG. The levels for wait times of the screening process were developed based on feedback from focus groups and are intended to incorporate the wait times experienced by individuals in rural and regional areas, as well as those receiving complicated or uncertain results. The levels for the false-positive rate reflect the accuracy of NIPT in detecting the three common trisomies (0.1%) [2] and recent evidence that the false-positive rate for rare autosomal trisomies can be as high as 55% [21]. The cost levels were based on the current price of NIPT (for three common trisomies) at AU$450 in Australia [5]. We included extreme values of AU$0, representing an 'ideal' and hypothetical publicly funded system, and AU$1000, reflecting a hypothetical commercial price for expanded NIPT (i.e., NIPT which tests for the broader range of conditions). All levels were reviewed by the EAG and were considered acceptable in light of the current evidence. The structure of the survey and information presented to participants prior to completing the choice tasks can be found within the Supplementary materials.

## 2.4 Cognitive Interviews

The DCE survey was tested through cognitive (think aloud) interviews to assess understanding and comprehension of the survey, using a convenience sample ($n = 10$). A number of changes were made based on the feedback from the cognitive interviews including formatting changes (e.g., creating space between the columns which represent the screening approaches; presenting the scenario in dot points) and changes to the wording of the scenario, question, and attribute levels to improve clarity (e.g., adding clarification that the focus of the survey is the screening test and not the diagnostic test). An example of the final choice task can be found in Fig. 1.

**Table 1** Attributes and levels presented in the choice tasks

| Attributes | Levels in screening approaches A and B | | | Levels in no screening approach |
|---|---|---|---|---|
| *What conditions does the screening test cover?* | A wide range of other rare conditions in addition to the three common chromosome conditions including Down syndrome | Three common chromosome conditions including Down syndrome | | None, screening test is not performed |
| *Chance of a false alarm*: The proportion of children without a chromosome condition, where the screening test suggests there is a chromosome condition | 0.1 of 100 babies | 5 of 100 babies | 55 of 100 babies | No chance of a false alarm |
| *Chance of a missed case*: The proportion of children with a chromosome condition, where the screening test suggests there is no chromosome condition | 0.1 of 100 babies | 5 of 100 babies | 10 of 100 babies | All cases are missed as there is no screening |
| *The proportion of screening tests that fail to provide a result* | None (0 of 100 tests) | 3 of 100 tests | 5 of 100 tests | None, screening test is not performed |
| *Does the screening test reveal the sex?* | Yes | No | | No, screening test is not performed |
| *Number of screening tests* | 1 | 2 | | None, screening test is not performed |
| *Wait time:*<br>From the first appointment with your family doctor until you decide to do no further testing or have a definitive answer | 2 weeks | 6 weeks | 10 weeks | 0 weeks |
| *Cost (AU$) of screening test(s):* Not covered by Medicare or Personal Health Insurance | $0 | $500 | $1000 | $0 |

### 2.5 Experimental Design

An online pilot survey was used to obtain priors on the first 35 respondents recruited through the web-panel provider. Ngene version 1.4.0 was used to generate a D-efficient design with 60 choice tasks in five blocks of 12 choice tasks. The DCE was carried out in two steps. In the first step, participants were presented with two alternatives and an opt-out option. The opt-out option aims to reflect a real-life situation where they can decide not to partake in the screening programme. If a participant decided to opt out, they were then presented with an additional question forcing them to choose between the two alternatives. The forced choice was included in case the opt-out option caused a significant decrease in the data available to analyse preferences [15]. A sample size of 328 participants was used for the full DCE. Although sample size calculations are not required for DCEs [22], the chosen sample size exceeds the minimum sample size using the rule of thumb method proposed by Orme, which accounts for two-way interactions ($n = 222$) [23]. See the Supplementary material for more information on survey design and sample size.

### 2.6 Analysis

Microsoft Excel was used to generate descriptive statistics and NLOGIT version 6 was used for the DCE analyses. Based on exploration of the pilot data, it was decided that participants who completed the survey in less than three minutes would be excluded from the main analysis. These respondents were considered to be 'potential bots', given that it was estimated to take 2–3 minutes to navigate the survey by clicking 'Next' as quickly as possible. To further minimise the risk of bots, respondents were excluded if they had a ReCAPTCHA score below 0.5 and failed the white text 'bot' question, which is written in the same colour as the background and cannot be seen by a person.

The initial analysis employed a multinomial logit model (MNL) as a baseline for developing more sophisticated models. Within the MNL model, all attributes were tested as categorical (effects coded) and continuous variables to establish the best model fit. The final model included variables *Conditions covered* and *Sex reveal* as categorical variables using effects coding, and all other attributes were coded as continuous variables. Although DCEs are commonly analysed using an MNL model, it does not allow preference heterogeneity to be assessed [24]. To overcome this limitation, the data were analysed using a mixed-logit panel model and latent class panel model.

A mixed logit model yields both a mean and standard deviation effect across the sample, reflecting the differences in preferences among respondents. The mixed logit model specified cost to have random parameters with a truncated triangular distribution, as a priori cost is known to have a negative coefficient. All other attributes were coded to have normally distributed random parameters. Dummy variables were created to distinguish between metropolitan and rural (remote and regional) respondents. These dummy variables were interacted with all attributes to assess how geographical location influenced preferences. Other sociodemographic characteristics (age, education, income, termination attitudes and gender) were effects coded and explored as main effects. The mixed logit analysis was conducted using 10,000 Halton draws. The final mixed logit model results are presented as the estimated β parameters, *p*-values (with the statistical significance threshold of $p < 0.05$) and the standard deviations (SD) and *p*-values and confidence intervals of the random parameters. The utility function and results for alternative model specifications are provided in the Supplementary materials.

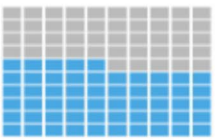
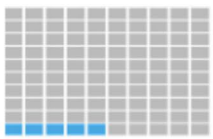
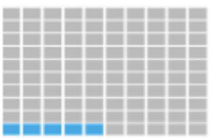
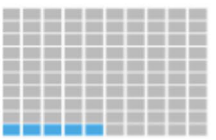
Latent class (LC) models with a different number of classes (one to eight) were also estimated to determine the ideal number of classes to fit the data [24]. The LC model with the best fit included four classes. For all models, model fit was compared using the Akaike information criterion (AIC), pseudo R2 and Log likelihood of model (LL) [15].

Marginal rates of substitution (trade-offs) were estimated for significant attributes ($p < 0.05$) as benefit/harm trade-offs and WTP estimates. These estimates were calculated using the results from the mixed logit model and calculated separately for metropolitan and rural groups (based on interactions between attributes and geographic group). Benefit/harm trade-offs were calculated for significant attributes in relation to wait time (weeks). This involved calculating the ratio of an attribute's parameter estimate (or difference between level estimates, if categorical) to the negative of the parameter estimate of wait time. The WTP estimates represent how much participants are willing to pay (in AU$) for specifc features of screening. This involved calculating the ratio of an attribute's parameter estimate (or difference between level estimates, if categorical) to the negative of the parameter estimate of cost [25]. An additional analysis was conducted to estimate the WTP to avoid an increase in the false-positive rate from 0.1% to 55%. This estimate is based on evidence regarding the false-positive rates associated with screening for three common trisomies [2] and a wide range of other conditions [21]. This analysis assumed a linear WTP and multiplied the WTP estimate for a unit change in the false-positive rate by 54.9 (the difference between 55% and 0.1%). A supplementary analysis was performed including 'potential bots', using a mixed logit model.

Q1/12

**Imagine you or your partner are expecting a baby, and you have an appointment with your local family doctor at 10 weeks. At this appointment, the family doctor suggests you or your partner undergo prenatal screening.**

- If you decide to undertake prenatal screening, and the results from the screening test suggest your unborn baby has a low chance of a chromosome condition, you will not be recommended further testing.
- If the results from the screening test suggest your unborn baby has a high chance of a chromosome condition or the test fails and does not give a result, you will be offered a diagnostic test to give a definitive yes or no answer. This test carries a small risk of miscarriage (0.3-1%)

| Features of each screening approach (All features apply) | Prenatal Screening Approach A | Prenatal Screening Approach B | No screening |
|---|---|---|---|
| What conditions does the screening test cover? | A wide range of other rare conditions in addition to the three common chromosome conditions including Down syndrome | Three common chromosome conditions including Down syndrome | None, screening test is not performed |
| Chance of a false alarm: The proportion of children without a chromosome condition, where the screening test suggests there is a chromosome condition. | 0.1 out of 100 babies  | 55 out of 100 babies  | No chance of a false alarm |
| Chance of a missed case: The proportion of children with a chromosome condition, where the screening test suggests there is no chromosome condition. | 5 out of 100 babies  | 5 out of 100 babies  | All cases are missed as there is no screening |
| The proportion of screening tests that fail to provide a result | None (0 out of 100 tests) | 5 out of 100 tests  | None, screening test is not performed |
| Does the screening test reveal the sex of the baby? | No | Yes | No, screening test is not performed |
| Number of screening tests | 1 | 2 | 0 |
| Wait time: From the first appointment with your family doctor until you either decide to not do further testing or have a definitive answer | 6 weeks *(outcome at week 16 of pregnancy)* | 2 weeks *(outcome at week 12 of pregnancy)* | 0 weeks |
| Cost of screening test(s): Not covered by Medicare or Personal Health Insurance | $500 | $500 | $0 |

| Prenatal Screening Approach A | Prenatal Screening Approach B | No screening |
|---|---|---|
| ○ | ○ | ○ |

**Fig. 1** Example of the final choice task

# 3 Results

## 3.1 Participants

In total, there were 374 eligible respondents, based on the inclusion criteria. Forty-six respondents were then excluded from the analysis, including 34 respondents who completed the survey in less than three minutes (potential bots), and 12 others who failed the additional quality control measures, including low ReCAPTCHA scores and responding to a white bot question. There were 328 respondents included within the main analysis, and the mean time to complete the survey was 17.6 minutes, falling within the expected range.

The sociodemographic characteristics of included respondents are reported in Table 2. There was a relatively even spread across gender, age ranges, and education status of respondents. The majority of respondents had no experience with prenatal screening or were unsure (63%). The sample consisted of 160 people (49%) living in a major city, 103 (31%) in inner regional locations, 61 in outer regional, remote or very remote locations (19%) and four respondents were unsure (1%). Metropolitan and rural (including inner regional, outer regional, remote and very remote locations) respondents were similar across the majority of sociodemographic characteristics. However, some differences were seen in age distributions and sex across metropolitan and rural respondents.

## 3.2 Mixed Logit Model

The mixed logit model had a log likelihood function of −2669, AIC/N of 1.581 and R2 of 0.292. The analysis is based on the three alternatives. Since we collected sufficient data, the forced choice was not analysed. The estimated coefficient for significant attributes ($p < 0.05$) had the expected sign providing support for the validity of the model. Results for the mixed logit model are discussed below and presented in Table 3. The supplementary analysis including 'potential bots' is presented in the Supplementary materials; the inclusion of these respondents did not have a substantial impact on the results.

### 3.2.1 Preferences

Respondents strongly favoured prenatal screening over no screening ($\beta = -3581$, $p$-value 0.000). Metropolitan respondents preferred a screening test with a lower false-positive rate, lower false-negative rate and lower cost. The conditions covered, inconclusive rate, sex reveal, number of tests and wait time were not found to be significant within the metropolitan group, and the confidence intervals ranged from negative to positive for each of these attributes. Within the rural group, a greater number of attributes were found to impact on preferences, with respondents preferring a test which covers a broader range of conditions, lower false-positive rate, lower false-negative rate, lower inconclusive rate, shorter wait time and lower cost. The number of tests and sex reveal were not found to be significant. A large number of attributes were found to have statistically significant and relatively large standard deviations, indicating preference heterogeneity. Although including sociodemographic characteristics as main effects improved the model fit, these factors were not statistically significant predictors.

## 3.3 Marginal Rates of Substitution

### 3.3.1 Benefit to Harm Trade Offs

Metropolitan respondents were willing to wait the longest to avoid an increase in the test cost of $100 (at 4 weeks), and the least amount of time to avoid a test with a 1% increase in the false-positive rate (at 0.6 weeks). Rural respondents were willing to wait the longest to screen for a wide range of conditions (instead of only the three trisomies—at 10.3 weeks), and the least amount of time to avoid a test with a 1% increase in the false-positive rate (at 0.5 weeks). The results can be found in Table 4.

### 3.3.2 Willingness to Pay

For metropolitan respondents, WTP was highest to avoid a 1% increase in the false-negative rate (at AU$30), and lowest to avoid a 1% increase in the false-positive rate (at AU$13). For rural respondents, WTP was highest to screen for a wide range of conditions (instead of only the three trisomies—at AU$323), and lowest to avoid a 1% increase in the false-positive rate (at AU$16). The results can be found in Table 5.

Assuming that WTP is linear (where respondents are willing to pay AU$16 for each 1% increase in the false-positive rate), respondents would be willing to pay AU$878 to avoid an increase in the false-positive rate from 0.1% to 55%.

## 3.4 Latent Class Model

The results were also analysed using latent class (LC) analysis. However, the LC model did not offer an improvement over the mixed logit models, and no significant predictors of class membership emerged. Therefore, the results for the LC model have not been discussed and are instead provided in the Supplementary materials.

**Table 2** Respondent characteristics ($N = 328$)

| Characteristics | Respondents | | | | | |
|---|---|---|---|---|---|---|
| | Rural | | Metropolitan | | Overall | |
| | *n* | % | *n* | % | *n* | % |
| *Age* | | | | | | |
| 18–24 | 43 | 26% | 22 | 14% | 65 | 20% |
| 25–29 | 36 | 21% | 19 | 12% | 55 | 17% |
| 30–34 | 48 | 29% | 43 | 27% | 91 | 28% |
| 35–39 | 18 | 11% | 26 | 16% | 44 | 13% |
| 40–45 | 23 | 14% | 49 | 31% | 73 | 22% |
| *Sex* | | | | | | |
| Male | 48 | 29% | 111 | 69% | 159 | 48.50% |
| Female | 119 | 71% | 49 | 31% | 168 | 51.20% |
| Non-binary | 1 | 1% | 0 | 0% | 1 | 0.30% |
| *State* | | | | | | |
| NSW | 47 | 28% | 51 | 32% | 98 | 30% |
| Vic | 54 | 32% | 61 | 38% | 115 | 35% |
| Qld | 39 | 23% | 13 | 8% | 52 | 16% |
| WA | 10 | 6% | 15 | 9% | 25 | 8% |
| NT | 1 | 1% | 1 | 1% | 2 | 1% |
| SA | 10 | 6% | 16 | 10% | 26 | 8% |
| ACT | 7 | 4% | 1 | 1% | 8 | 2% |
| *Interested in becoming pregnant (or partner)* | | | | | | |
| Yes | 122 | 73% | 111 | 70% | 233 | 71% |
| No | 46 | 27% | 48 | 30% | 94 | 29% |
| *Have been pregnant (or partner)* | | | | | | |
| Yes | 107 | 64% | 97 | 61% | 204 | 62% |
| No | 61 | 36% | 62 | 39% | 124 | 38% |
| *Have undergone prenatal screening (or partner)* | | | | | | |
| Yes | 59 | 35% | 55 | 35% | 114 | 35% |
| No/ unsure | 109 | 65% | 105 | 65% | 214 | 65% |
| *Family member with a chromosome (genetic) condition* | | | | | | |
| Yes | 13 | 8% | 14 | 9% | 27 | 8% |
| No/unsure | 155 | 92% | 145 | 91% | 300 | 92% |
| *Education* | | | | | | |
| Non-university | 111 | 69% | 55 | 36% | 148 | 47% |
| University | 49 | 31% | 99 | 64% | 166 | 53% |
| *Household income before tax (AU$)* | | | | | | |
| 0–$18,200 per year | 10 | 6% | 0 | 0% | 10 | 3% |
| $18,201–$45,000 per year | 21 | 13% | 12 | 8% | 33 | 10% |
| $45,001–$120,000 per year | 69 | 42% | 56 | 36% | 125 | 39% |
| $120,001–$180,000 per year | 42 | 26% | 57 | 37% | 99 | 31% |
| Over $180,000 per year | 15 | 9% | 22 | 14% | 37 | 11% |
| Prefer not to answer/don't know | 6 | 4% | 8 | 5% | 17 | 5% |
| *Agree with terminating a pregnancy* | | | | | | |
| No | 42 | 25% | 45 | 29% | 87 | 27% |
| Neutral | 31 | 19% | 37 | 24% | 68 | 21% |
| Yes | 93 | 56% | 74 | 47% | 167 | 52% |

"Rural" includes inner regional, outer regional, remote and very remote locations

**Table 3** Mixed logit model results, by respondent geographical location

| Attribute | Mean | | | | Standard deviation | | | |
|---|---|---|---|---|---|---|---|---|
| | Coefficient | 95% CI | | *p*-value | Coefficient | 95% CI | | *P* value |
| No screening | − 3.581** | − 4.540 | − 2.623 | 0.000 | − 2.246 | − 5.792 | 1.300 | 0.214 |
| *Metropolitan respondents* | | | | | | | | |
| Conditions covered (broad range) | 0.072 | − 0.015 | 0.16 | 0.104 | 0.325 | − 0.006 | 0.656 | 0.054 |
| Conditions covered (three trisomies) – omitted level | − 0.072 | | | | | | | |
| False-positive rate (%) | **− 0.013**** | **− 0.019** | **− 0.008** | **0.000** | **0.023** | **− 0.016** | **0.029** | **0.000** |
| False-negative rate (%) | **− 0.029**** | **− 0.048** | **− 0.010** | **0.002** | **0.034** | **− 0.009** | **0.077** | **0.125** |
| Inconclusive rate (%) | 0.001 | − 0.039 | 0.040 | 0.978 | 0.097** | 0.026 | 0.169 | 0.008 |
| Sex revealed | − 0.012 | − 0.091 | 0.066 | 0.759 | 0.185* | 0.029 | 0.341 | 0.020 |
| Sex not revealed – omitted level | 0.012 | | | | | | | |
| Number of tests | 0.069 | − 0.081 | 0.218 | 0.368 | 0.003 | − 2.898 | 2.905 | 0.998 |
| Wait time (weeks) | − 0.023 | − 0.050 | 0.003 | 0.088 | 0.051* | 0.000 | 0.102 | 0.048 |
| Cost (AU$) | **− 0.001**** | **− 0.001** | **− 0.001** | **0.000** | **0.001** | **0.001** | **0.001** | **0.000** |
| *Rural respondents (regional, remote, and very remote)* | | | | | | | | |
| Conditions covered (broad range) | **0.162**** | **0.065** | **0.258** | **0.001** | **0.476**** | **0.231** | **0.721** | **0.000** |
| Conditions covered (three trisomies) – omitted level | − 0.162 | | | | | | | |
| False-positive rate (%) | **− 0.016**** | **− 0.022** | **− 0.010** | **0.000** | **0.025** | **0.019** | **0.031** | **0.000** |
| False-negative rate (%) | **− 0.022*** | **− 0.041** | **0.000** | **0.046** | **0.048** | **0.021** | **0.075** | **0.000** |
| Inconclusive rate (%) | **− 0.051**** | **− 0.087** | **− 0.016** | **0.005** | **0.074** | **− 0.001** | **0.149** | **0.055** |
| Sex revealed | − 0.031 | − 0.105 | 0.043 | 0.415 | 0.148** | 0.011 | 0.285 | 0.034 |
| Sex not revealed – omitted level | − 0.031 | | | | | | | |
| Number of tests | 0.023 | − 0.127 | 0.173 | 0.762 | 0.038 | − 1.034 | 1.110 | 0.945 |
| Wait time (weeks) | **− 0.031*** | **− 0.060** | **− 0.003** | **0.032** | **0.046** | **− 0.002** | **0.094** | **0.059** |
| Cost (AU$) | **− 0.001**** | **− 0.001** | **− 0.001** | **0.000** | **0.001** | **0.001** | **0.001** | **0.000** |
| *Sociodemographic characteristics* | | | | | | | | |
| Age (> 35 years) | 0.001 | − 0.549 | 0.550 | 0.998 | 0.088 | − 4.510 | 4.685 | 0.970 |
| Male | − 0.456 | − 1.034 | 0.122 | 0.122 | 1.268 | − 3.975 | 6.511 | 0.636 |
| University degree | − 0.119 | − 0.672 | 0.433 | 0.672 | 0.105 | − 4.154 | 4.363 | 0.962 |
| Family member with a genetic condition | 0.565 | − 0.241 | 1.372 | 0.170 | 0.978 | − 4.519 | 4.646 | 0.978 |
| Against termination | − 0.357 | − 0.882 | 0.168 | 0.183 | 1.692 | − 1.971 | 5.355 | 0.365 |
| Low income | 0.748 | − 1.602 | 3.098 | 0.533 | 1.227 | − 4.843 | 7.298 | 0.692 |

Significant attributes (based on the *p*-value of the mean) have been bolded

*CI* confidence interval

*Significance at 1%

**Significance at 5%

**Table 4** Benefit/harm trade-offs (wait time of the screening process)

| Willing to wait additional weeks to: | Metropolitan respondents | Rural respondents |
|---|---|---|
| Screen for a wide range of conditions instead of only the three common trisomies | Not significant | 10.3 weeks |
| Avoid a 1% increase in the false-positive rate | 0.6 weeks | 0.5 weeks |
| Avoid a 1% increase in the false-negative rate | 1.25 weeks | 0.7 weeks |
| Avoid a 1% increase in the inconclusive rate | Not significant | 1.64 weeks |
| Avoid a $100 increase in the cost | 4 weeks | 3 weeks |

Wait time is from the first appointment with your family doctor until you decide to do no further testing or have a definitive answer

**Table 5** Willingness to pay (AU$)

| Willingness to pay to: | Metropolitan respondents | Rural respondents |
|---|---|---|
| Screen for a wide range of conditions instead of only the three common trisomies | Not significant | $323 |
| Avoid a 1% increase in the false-positive rate | $13 | $16 |
| Avoid a 1% increase in the false-negative rate | $30 | $22 |
| Avoid a 1% increase in the inconclusive rate | Not significant | $51 |
| Avoid waiting an extra week to receive the results | Not significant | $31 |

## 4 Discussion

This DCE investigated Australian preferences for prenatal screening in both rural and metropolitan locations across the country. The findings revealed that Australians have a strong preference for undergoing prenatal screening. Metropolitan respondents' preferences were significantly influenced by the accuracy and cost of the screening test. In contrast, preferences of rural respondents were influenced by a broader range of factors including the scope of conditions covered, test accuracy, wait times and cost. The number of screening tests and revealing the biological sex of the foetus were not significant features within either group. In scenarios with high levels of false-positive rates, consistent with expanded NIPT, rural respondents prioritised the false-positive rate over the scope of conditions covered by the screening test. Rural and metropolitan respondents displayed similar preferences for attributes significant to both groups, where benefit to harm trade-offs and willingness to pay results were comparable.

Rural preferences for prenatal screening were influenced by a broader range of prenatal screening features compared to the metropolitan group. Rural respondents preferred a test which screened for a wide range of conditions, a lower inconclusive rate and shorter wait times. In contrast, metropolitan preferences were not found to be significantly influenced by these features of screening. It was anticipated that rural respondents would have a greater number of concerns given the additional challenges encountered during pregnancy by individuals in rural Australia, including difficulties accessing prenatal screening and follow-up services due to location and socioeconomic factors [7, 26–29]. Additionally, there are lower levels of support and resources available to raise a child with a disability, increasing the implications of screening [29]. As expected, wait times significantly impacted the preferences of rural respondents. This is likely due to rural communities being familiar with the effects of wait times [30], whereas for metropolitan participants, 10 weeks may not seem like a realistic scenario. A surprising result was the similarity in the influence of cost between both groups, along with comparable WTP estimates for different features of screening. We expected cost to be a greater concern to rural respondents given they generally have a lower socioeconomic status, and the cost of prenatal screening and follow-up services present greater risk to their financial protection. The similarity in results could be due to the similar income distribution across respondent groups, and/or due to the indirect costs of screening (e.g., travel, accommodation and resulting loss of income) not being considered within the DCE. These findings are consistent with the conclusion that the lower uptake of NIPT in rural Victoria is likely driven by socioeconomic factors, rather than valuing the features of screening less than metropolitan communities [31]. Further research is needed to estimate current uptake of NIPT in rural areas across Australia and to understand whether publicly funded NIPT could help reduce inequities. These findings are specific to the Australian context; however, they may be relevant for other Western countries which do not publicly fund NIPT.

Our results suggest a complex interplay between preferences for the scope of the test and the false-positive rate. Interestingly, metropolitan preferences were not significantly influenced by conditions covered, unlike within the rural group. The qualitative literature describes two models of thought regarding testing for a broader range of conditions. The first model is underpinned by the desire "*to have a fuller understanding of the health of their baby and their pregnancy*" and resolve uncertainty [6]. While the second model revolves around not all information being beneficial, with increased information leading to results that are unanticipated and not reassuring [6, 12]. These divided views are also present when considering genomic screening in a broader context [32]. Our findings suggest the rural group aligns more with the first model, valuing comprehensive information to resolve uncertainties. This preference may be influenced by the limited support available for raising a child with a disability in rural areas. Meanwhile, the metropolitan group shows more variability in their decision making, possibly reflecting the broader range of experiences and resources available in urban settings. However, rural respondents only prioritised the scope of conditions covered when false positives were low. In reality, low false-positive rates are consistent with detecting only the three common trisomies [2]. When considering a broad range of conditions,

the false-positive rate can be as high as 55% [21]. At this extreme value, rural respondents prioritised the false-positive rate over the scope of conditions covered.

Within the Australian context, clinicians have raised concerns about expanding the scope of NIPT. This is due to the potentially high levels of false-positive rates, variable phenotypes and lack of resources in the Australian health system to appropriately deliver and manage such results [6, 33]. In WA, preferences for an increased scope of testing (100–400 genetic disorders compared to three common trisomies and sex chromosome conditions) were found to be of similar magnitude to the preference for high accuracy (positive predictive value) [13]. Internationally, studies have shown varying priorities amongst women. A DCE conducted in the Netherlands found conditions covered to be the most important attribute; however, only low levels of false-positive rates were considered [34]. In contrast, two international DCEs found respondents prioritised a relatively small reduction in accuracy over the scope of the test [35, 36]. An international survey found that across multiple countries (including Australia), all countries except China preferred a broad rather than a targeted test, although this was not traded off against accuracy [9]. Our findings demonstrate that the Australian public preferences align with clinicians' concerns when they are presented with high false-positive rates, emphasising the importance of communicating the accuracy of the prenatal screening test.

This study quantifies the impact of intermediate and process outcomes on preferences through WTP estimates. These estimates ranged from AU$13 to avoid a one percent increase in the false-positive rate to AU$51 to avoid a one percent increase in the inconclusive rate. These findings align with the qualitative literature, which highlight the stress and anxiety associated with wait times and the uncertainty regarding false or inconclusive results [37]. Qualitative studies have reported that anxiety around wait times stem from the concern that pregnant individuals might be forced to make rapid healthcare decisions that affect them, their children and their family [38]. In line with our results, a recent DCE conducted in WA found women were willing to pay between AU$281 and AU$1256 to avoid a 49% decrease in accuracy, noting they were looking at a different application of testing (even larger scope including single gene disorders) [13]. A DCE conducted in the Netherlands reported similar, although somewhat larger, WTP estimates compared to our results, with women willing to pay 23 euros (~AU$37) for results to be received one week earlier and 112 euros (~AU$182) for a percentage point lower false-positive rate [34]. A DCE conducted in Singapore calculated even larger WTP estimates [39]. The importance of process and intermediate outcomes is also supported within the broader literature of genetic and genomic testing, with three DCEs finding that Australians are willing to pay AU$2340 to be very likely to improve the process of medical care (compared to not likely) in the context in paediatric genomic sequencing, AU$1625 in the context of symptomatic adult genomic sequencing and AU$1177 in the context of at-risk adult genomic sequencing [40]. These findings collectively highlight the importance of considering both intermediate and process outcomes in policy decisions.

The WTP estimates presented in this study offer a pathway to directly integrate the impacts of process and intermediate outcomes into economic evaluations. Considering the current estimated cost of NIPT is AU$450 [5], it is likely that including these estimates into economic evaluations will influence the cost effectiveness of NIPT. Various options have been proposed in the literature. The more conventional approach is to incorporate WTP estimates through a cost-benefit analysis [16]. A less conventional approach would be to include the WTP estimates within the cost side of a cost-utility analysis [41]. Among economic evaluations of NIPT, it is rare to consider the associated intermediate and process outcomes [42]. Evaluations which have attempted to include these outcomes have relied on a time trade-off study, which found only minor decrements in utility [43]. This contrasts with qualitative literature that suggests these outcomes have considerable impact. The study authors hypothesise that the discrepancies may be due to the time trade-off methodology used, which involved multiple complex scenarios and a trade-off with death. The challenge of including process and intermediate outcomes into economic evaluations is not limited to prenatal screening but is present more broadly in genomic testing [44]. How to include evidence from stated preference research in health technology assessments is also the subject of current debate [16, 45–47]. Further research is needed to explore the implications of including WTP estimates for process and intermediate outcomes within economic evaluations, and the resulting impacts on decision making.

## 5 Limitations

A number of limitations should be considered when interpreting the results of this study, including the population, recruitment methods and sample size. This study includes members of the general public who have an interest in pregnancy. Whilst this means respondents were more likely to be engaged in the content of the task, it also means that the WTP estimates may not be representative of the general population. This has implications for public funding decisions, given that Australian guidelines currently recommend using public preferences rather than patient preferences, noting our sample is broader than the patient population [48]. We would expect the WTP estimates to be lower if individuals with no interest in pregnancy were included. However, these estimates are consistent, although somewhat lower, than a DCE conducted in

WA, which includes all women aged between 18 and 45 years [13]. Although steps were taken to avoid bots, including trap questions, ReCAPTCHA scores and removing respondents who took less than 3 minutes to complete the survey, there remains a possibility of their occurrence. The focus groups were conducted in one state (New South Wales), while the DCE was conducted across Australia. The sample size was substantial for the primary analysis; however, the sample size limited our ability to analyse preferences for different subgroups (e.g., different income levels, age, termination attitudes), which is likely to explain why the latent class model did not offer improvements and why the sociodemographic predictors in the mixed logit model were not significant. Lastly, this survey required relatively high levels of literacy and excluded people who could not speak English.

## 6 Conclusion

This study explores preferences for prenatal screening among Australians in both rural and metropolitan areas to assist with the development of an equitable implementation model. While metropolitan preferences were shaped by the accuracy and cost of screening tests, rural preferences were influenced by a broader range of screening features. This study quantifies the impact of intermediate and process outcomes on preferences through willingness to pay estimates, whilst accounting for differences in preferences between metropolitan and rural communities. These estimates highlight the significant value that individuals place on factors such as reduced waiting times and decreased false-positive rates. Incorporating these estimates into economic evaluations is likely to have implications for the cost effectiveness of prenatal screening and to impact policy decisions that rely on such analyses.

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## Declarations

**Credit category** Conceptualisation: A.S., S.N., A.P., K.H.; Data curation: A.S; Formal analysis: A.S.; Funding acquisition: A.S.; Investigation: Not applicable; Methodology: A.S., S.N., A.P., K.H.; Project administration: A.S., S.N., A.P., K.H.; Resources: Not applicable; Software: NA; Supervision: S.N., A.P., K.H.; Validation: NA; Visualisation: NA; Writing-original draft: A.S., S.N., A.P., K.H.; Writing-review & editing: A.S., S.N., A.P., K.H.

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**Competing interests** Authors declare no competing interests

**Ethics declaration** This research has been approved by the Human Ethics Committee at the University of Sydney [2023/170].

**Consent to participate** Consent was obtained by all participants prior to starting the survey.

**Consent for publication** Consent was obtained by all participants prior to starting the survey.

**Availability of data and material** Data used to support the findings of this study are available from the corresponding author upon reasonable request.

**Code availability** Available from the corresponding author upon reasonable request.



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## Supplementary materials

### Section A. Structure of the survey

1. An introduction to the study and consent
2. Questions about sociodemographic characteristics related to quotas and exclusions, as well as previous experiences with prenatal testing
3. Instructions for the DCE task, followed by the DCE choice tasks
4. Questions on other socio-demographic characteristics, health attitudes and health care experiences which may impact preferences
5. Open ended question to collect 'any other' information

### Section B. Information provided to participants prior to completing the choice task

Here is some information about prenatal screening

*Information on prenatal screening*

Prenatal screening involves a combination of tests to see if your unborn baby is more or less likely to have one of the three common chromosome conditions (Down syndrome, Edwards syndrome and Patau syndrome).

People with Down syndrome can have an intellectual disability and some additional health concerns. Edwards syndrome and Patau syndrome are less common than Down syndrome. Babies born with these conditions have serious health conditions and often don't live beyond the first weeks of life. It is also possible to test for a large number of chromosome conditions including sex chromosome conditions and other rare conditions. The screening test can also determine the sex of the unborn baby.

Prenatal screening tests tell you the **CHANCE** of your unborn baby having one of the conditions listed above. It will not give you a definite (yes or no) answer. You will receive either

a **high chance result (more likely to have the condition)** or a **low chance result (less likely to have the condition)**. It is also possible for the test to fail and not give a result.

If you receive a low chance result, you will not be recommended to have further testing. If you receive a high chance result or the test fails, you will be offered a diagnostic test to give you a definite yes or no answer. The diagnostic test involves inserting a needle into the mother's tummy. This test has a small risk of miscarriage, between 0.3% *(3 out of 1000 chance)* to 1% *( 10 out of 1000 chance).* The usual full length of pregnancy is 40 weeks.

**Click next to get information on the survey questions**

*Information on the attributes and levels*

The survey questions will ask you to **choose between two different prenatal screening approaches and no screening**. We are not asking about the diagnostic test. You choose the screening option that you would prefer.

You will be asked to complete 12 survey questions. The questions look similar BUT they are different. The prenatal screening approach will vary based on the following features:

*What conditions does the screening test cover?*

The screening test(s) may look at the common chromosome conditions (including Down syndrome), or the test can also include a wider range of other rare chromosome conditions.

*Chance of a false alarm*

The proportion of children without a chromosome condition, where the screening test suggests there is a chromosome condition (i.e. the screening test says your baby has a high chance of having a chromosome condition and these results are wrong).

*Chance of a missed case*

The proportion of children with a chromosome condition, where the screening test suggests there is no chromosome condition (i.e. the screening tests says your baby has a low chance of having a chromosome condition and these results are wrong).

*The proportion of screening tests that fail to provide a result*

Some screening tests will fail and not be able to give you a result.

*Does the screening test reveal the sex of the baby?*

Some screening tests are able to reveal the sex of your unborn baby.

*Number of screening tests*

You may be required to have one or two screening tests. For each screening test, you will go to see your obstetrician who will perform the test.

*Wait time (entire screening process)*

This covers the wait time from the first visit to you local family doctor until you have either decided to not do further testing or you receive a final definitive answer from the diagnostic test.

*Cost of screening test(s)*

The cost of the screening test(s) will vary between free and $1000. This cost is not able to be reimbursed through Medicare or Private Health Insurance. No other costs are considered.

**Click next to begin the survey** (if you're on a mobile phone, please switch it to landscape mode)

## Section C. Survey design and sample size

Ngene version 1.4.0 was used to generate a D-efficient design with 60 choice tasks divided into five blocks, each containing twelve choice tasks with two alternatives per task and an opt-out option. The DCE was conducted in two steps. Initially, participants were presented with two profiles and an opt-out option to simulate a real-life scenario where they might choose not to participate in the screening program. If a participant opted out, they were subsequently required to choose between the two profiles. Participants were randomly assigned one of the five blocks of choice questions. The DCE study questionnaire included background information, an explanation of the choice questions, definitions of attributes and levels, twelve choice questions, and attribute-related and sociodemographic questions.

Pilot study data provided priors for the experimental design, reported as D-efficiency (lower is better) and an S-estimate (a proxy for sample size). In this study, the D-efficiency of the design was 0.000873, and the S-estimate was 815. The high S-estimate was influenced by *wait time* with other S-estimates ranging from 3 (*cost*) to 183 (*number of tests*). Alternative experimental designs were considered, including varying prior estimates for *wait time* and altering constraints for *wait time* within the survey. These changes resulted in minimal variation in the S-estimates, so they were not adopted. Some authors suggest using 20 respondents per block (n=100), although this does not account for covariates or two-way interactions.[2] An alternative method is the rule of thumb method proposed by Orme, which can account for two way interactions.[3] The formula is as follows:

$N > (500 \times c) / (t \times a)$

Where t = the number of choice tasks, a = the number of alternatives, and when considering two-way interactions, c = largest product of any two attributes. In our DCE, N> 222. Our sample size of 328 exceeds this recommendation.

## Section D. Utility function

The utility functions for the final mixed logit model were specified as follows:

U(AppA) = cond_R * cond_R + cond_M * cond_M
+ FP_R* FP_R + FP_M * FP_M
+ FN_R * FN_R + FN_M * FN_M
+ IncR_R * IncR_R + IncR_M * IncR_M
+ Sex_R * Sex_R + Sex_M * Sex_M
+ Ntest_R * Ntest_R + Ntest_M * Ntest_M
+ Wait_R * Wait_R + Wait_M * Wait_M
+ Cost_R * Cost_R + Cost_M * Cost_M
+ AGE * AGE_OVER + male * Male + remote * Rural + fam * family + uni * Uni + term * Term_nan + Risk*risk_see + incomeL * Y_low

U(AppB) = cond_R * cond_R + cond_M * cond_M
+ FP_R* FP_R + FP_M * FP_M
+ FN_R * FN_R + FN_M * FN_M
+ IncR_R * IncR_R + IncR_M * IncR_M
+ Sex_R * Sex_R + Sex_M * Sex_M
+ Ntest_R * Ntest_R + Ntest_M * Ntest_M
+ Wait_R * Wait_R + Wait_M * Wait_M
+ Cost_R * Cost_R + Cost_M * Cost_M
+ AGE * AGE_OVER + male * Male + remote * Rural + fam * family + uni * Uni + term * Term_nan + Risk*risk_see+ incomeL * Y_low

U(NoApp) = NONE

## Section E. Additional analyses

*Mixed logit analysis including potential bots*

This analysis differs from the main analysis by including respondent who took less than 3 minutes to complete the survey (n=34). In comparison to the main analysis, the significance and direction of all attributes are the same with the exception of the false negative rate in the rural group. See results in **Table 33**.

**Table 33. Additional analysis: mixed logit model including potential bots**

| CHOICE | Coefficient | Standard Error | z | P-value* | Lower CI | Upper CI |
|---|---|---|---|---|---|---|
| **Random parameters in utility functions** | | | | | | |
| COND_R | .31155*** | .08524 | 3.65 | .0003 | .14447 | .47862 |
| COND_M | .15062 | .07416 | 2.03 | .0423 | .00526 | .29598 |
| FP_R | -.01398*** | .00237 | -5.90 | .0000 | -.01863 | -.00934 |
| FP_M | -.01084*** | .00245 | -4.43 | .0000 | -.01564 | -.00604 |
| FN_R | -.01274 | .00861 | -1.48 | .1391 | -.02962 | .00414 |
| FN_M | -.02528*** | .00793 | -3.19 | .0014 | -.04082 | -.00973 |
| INCR_R | -.04301*** | .01595 | -2.70 | .0070 | -.07428 | -.01174 |
| INCR_M | -.00384 | .01744 | -.22 | .8259 | -.03802 | .03034 |
| SEX_R | -.02491 | .03514 | -.71 | .4784 | -.09379 | .04396 |
| SEX_M | .01136 | .03496 | .32 | .7452 | -.05716 | .07989 |
| NTEST_R | .01877 | .06487 | .29 | .7723 | -.10838 | .14592 |
| NTEST_M | .05368 | .06676 | .80 | .4213 | -.07717 | .18453 |
| WAIT_R | -.03415*** | .01253 | -2.73 | .0064 | -.05871 | -.00959 |
| WAIT_M | -.02114* | .01213 | -1.74 | .0815 | -.04492 | .00264 |
| COST_R | -.00096*** | .6452D-04 | -14.84 | .0000 | -.00108 | -.00083 |
| COST_M | -.00081*** | .6291D-04 | -12.90 | .0000 | -.00093 | -.00069 |
| NONE | -4.02830*** | .32331 | -12.46 | .0000 | -4.66197 | -3.39462 |
| **Distributions of RPs. Std.Devs or limits of triangular** | | | | | | |
| NsCOND_R | .39420*** | .12270 | 3.21 | .0013 | .15372 | .63469 |
| NsCOND_M | .22673 | .19565 | 1.16 | .2465 | -.15673 | .61019 |
| NsFP_R | .02326*** | .00260 | 8.95 | .0000 | .01817 | .02835 |
| NsFP_M | .02114*** | .00281 | 7.53 | .0000 | .01563 | .02664 |
| NsFN_R | .04146*** | .01317 | 3.15 | .0016 | .01564 | .06728 |
| NsFN_M | .01991 | .02969 | .67 | .5024 | -.03827 | .07809 |
| NsINCR_R | .06729* | .03726 | 1.81 | .0709 | -.00573 | .14031 |

| | | | | | | |
|---|---|---|---|---|---|---|
| NsINCR_M | .08051** | .03385 | 2.38 | .0174 | .01416 | .14686 |
| NsSEX_R | .19564*** | .05709 | 3.43 | .0006 | .08375 | .30754 |
| NsSEX_M | .17306** | .07152 | 2.42 | .0155 | .03289 | .31323 |
| NsNTEST_ | .04734 | .57815 | .08 | .9347 | -1.08582 | 1.18050 |
| NsNTEST1 | .00200 | 1.97729 | .00 | .9992 | -3.87342 | 3.87741 |
| NsWAIT_R | .03837 | .02493 | 1.54 | .1238 | -.01050 | .08724 |
| NsWAIT_M | .05692*** | .02065 | 2.76 | .0058 | .01644 | .09739 |
| TsCOST_R | .00096*** | .6452D-04 | 14.84 | .0000 | .00083 | .00108 |
| TsCOST_M | .00081*** | .6291D-04 | 12.90 | .0000 | .00069 | .00093 |
| NONE | 3.44176*** | .25726 | 13.38 | .0000 | 2.93754 | 3.94599 |

Abbreviations: COND = condition, FP = false positive, FN = false negative, INCR = inconclusive, NTEST = number of tests, WAIT = waiting time, COST = cost, R = rural, M = metropolitan, Ns = standard deviation, Ts = triangular distributionNotes:
Log likelihood function -3180.92285; Chi squared [ 32](P= .000) 2475.39155; McFadden Pseudo R-squared .2801092; Inf.Cr.AIC = 6425.8 AIC/N = 1.598
***, **, * ==> Significance at 1%, 5%, 10% level.

*Latent class analysis (four classes)*

A latent class model with four classes was found to have the best model fit. Results presented in

**Table 34**.

**Table 34. Latent class analysis (four classes)**

| CHOICE | Coefficient | Standard Error | z | P-value* | Lower CI | Upper CI |
|---|---|---|---|---|---|---|
| **Random utility parameters in latent class -->> 1** | | | | | | |
| CONDS\|1 | .85131*** | .12435 | 6.85 | .0000 | .60758 | 1.09504 |
| FALSEP\|1 | -.05804*** | .00484 | -11.99 | .0000 | -.06753 | -.04855 |
| FALSEN\|1 | -.04169*** | .01512 | -2.76 | .0058 | -.07134 | -.01205 |
| INCONC\|1 | .13781*** | .02741 | 5.03 | .0000 | .08409 | .19152 |
| SEX\|1 | -.07007 | .06070 | -1.15 | .2483 | -.18904 | .04890 |
| NUMBER\|1 | 1.12365*** | .12084 | 9.30 | .0000 | .88681 | 1.36049 |
| WWAIT\|1 | .02200 | .01800 | 1.22 | .2215 | -.01327 | .05728 |
| SCOST\|1 | -.00057*** | .00015 | -3.72 | .0002 | -.00087 | -.00027 |
| **Random utility parameters in latent class -->> 2** | | | | | | |
| CONDS\|2 | -.19147 | .20550 | -.93 | .3515 | -.59425 | .21132 |
| FALSEP\|2 | -.01597*** | .00340 | -4.70 | .0000 | -.02263 | -.00931 |
| FALSEN\|2 | .05693*** | .02155 | 2.64 | .0082 | .01470 | .09916 |
| INCONC\|2 | .14355*** | .04217 | 3.40 | .0007 | .06089 | .22621 |
| SEX\|2 | -.00204 | .11095 | -.02 | .9853 | -.21951 | .21543 |
| NUMBER\|2 | .98243*** | .14431 | 6.81 | .0000 | .69959 | 1.26527 |
| WWAIT\|2 | .06868** | .03019 | 2.28 | .0229 | .00952 | .12784 |
| SCOST\|2 | -.00464*** | .00042 | -11.09 | .0000 | -.00546 | -.00382 |
| **Random utility parameters in latent class -->> 3** | | | | | | |
| CONDS\|3 | .28520*** | .05252 | 5.43 | .0000 | .18226 | .38814 |
| FALSEP\|3 | .00649*** | .00111 | 5.82 | .0000 | .00430 | .00867 |
| FALSEN\|3 | .01503** | .00587 | 2.56 | .0105 | .00352 | .02654 |
| INCONC\|3 | .03149*** | .01091 | 2.89 | .0039 | .01010 | .05288 |
| SEX\|3 | -.01768 | .02310 | -.77 | .4442 | -.06296 | .02760 |
| NUMBER\|3 | .45281*** | .04190 | 10.81 | .0000 | .37069 | .53492 |
| WWAIT\|3 | .01740** | .00879 | 1.98 | .0479 | .00016 | .03463 |
| SCOST\|3 | .00017*** | .5380D-04 | 3.13 | .0018 | .00006 | .00027 |
| **Random utility parameters in latent class -->> 4** | | | | | | |
| CONDS\|4 | .72069 | 5.38063 | .13 | .8934 | -9.82515 | 11.26653 |
| FALSEP\|4 | -.03416 | .38069 | -.09 | .9285 | -.78030 | .71198 |
| FALSEN\|4 | -.25176 | .47806 | -.53 | .5984 | -1.18875 | .68522 |
| INCONC\|4 | .01721 | 1.38034 | .01 | .9901 | -2.68820 | 2.72262 |
| SEX\|4 | -.18723 | 1.06821 | -.18 | .8609 | -2.28088 | 1.90643 |
| NUMBER\|4 | -.86286 | 3.71769 | -.23 | .8165 | -8.14941 | 6.42368 |
| WWAIT\|4 | -.19120 | .95638 | -.20 | .8415 | -2.06567 | 1.68327 |
| SCOST\|4 | -.00111 | .00635 | -.18 | .8608 | -.01357 | .01134 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **This is THETA(01) in class probability model** | | | | | | |
| _ONE\|1 | -.96942 | 1.40029 | -.69 | .4888 | -3.71394 | 1.77511 |
| _OVER3\|1 | -.29084 | 1.14655 | -.25 | .7998 | -2.53803 | 1.95636 |
| _RURAL\|1 | .11577 | .70183 | .16 | .8690 | -1.25980 | 1.49133 |
| _YHIGH\|1 | 2.35380* | 1.37387 | 1.71 | .0867 | -.33893 | 5.04653 |
| _TERMN\|1 | -1.29162 | .91449 | -1.41 | .1578 | -3.08400 | .50075 |
| _UNI_D\|1 | -.00890 | .85667 | -.01 | .9917 | -1.68794 | 1.67014 |
| _FAM_D\|1 | 1.31275 | 1.18296 | 1.11 | .2671 | -1.00582 | 3.63132 |
| **This is THETA(02) in class probability model** | | | | | | |
| _ONE\|2 | -.94637 | 1.55663 | -.61 | .5432 | -3.99730 | 2.10457 |
| _OVER3\|2 | .36882 | 1.12925 | .33 | .7440 | -1.84447 | 2.58211 |
| _RURAL\|2 | .23690 | .74098 | .32 | .7492 | -1.21539 | 1.68920 |
| _YHIGH\|2 | 1.67855 | 1.30803 | 1.28 | .1994 | -.88514 | 4.24224 |
| _TERMN\|2 | -.63677 | .90978 | -.70 | .4840 | -2.41991 | 1.14636 |
| _UNI_D\|2 | -.09199 | .89249 | -.10 | .9179 | -1.84124 | 1.65726 |
| _FAM_D\|2 | 1.11021 | 1.30523 | .85 | .3950 | -1.44799 | 3.66841 |
| **This is THETA(03) in class probability model** | | | | | | |
| _ONE\|3 | 1.76880 | 1.24147 | 1.42 | .1542 | -.66444 | 4.20204 |
| _OVER3\|3 | -.13489 | 1.08190 | -.12 | .9008 | -2.25537 | 1.98559 |
| _RURAL\|3 | .17836 | .64267 | .28 | .7814 | -1.08125 | 1.43797 |
| _YHIGH\|3 | 1.47137 | 1.26929 | 1.16 | .2464 | -1.01640 | 3.95913 |
| _TERMN\|3 | -.38446 | .88064 | -.44 | .6624 | -2.11048 | 1.34155 |
| _UNI_D\|3 | -.59884 | .82829 | -.72 | .4697 | -2.22226 | 1.02458 |
| _FAM_D\|3 | .11279 | 1.04142 | .11 | .9138 | -1.92835 | 2.15393 |
| **This is THETA(04) in class probability model** | | | | | | |
| _ONE\|4 | 0.0 | (Fixed Parameter) | | | | |
| _OVER3\|4 | 0.0 | (Fixed Parameter) | | | | |
| _RURAL\|4 | 0.0 | (Fixed Parameter) | | | | |
| _YHIGH\|4 | 0.0 | (Fixed Parameter) | | | | |
| _TERMN\|4 | 0.0 | (Fixed Parameter) | | | | |
| _UNI_D\|4 | 0.0 | (Fixed Parameter) | | | | |
| _FAM_D\|4 | 0.0 | (Fixed Parameter) | | | | |

Abbreviations: CONDS = conditions, FALSEP = false positive, FALSEN = false negative, INCONC = inconclusive, NUMBER = number of tests, WWAIT = waiting time, SCOST = screening cost, _ONE = constant term, _OVER3 = over 3 (age), _RURAL = rural location, _YHIGH = high income, _TERMN = termination attitudes, *UNI*D = university degree, *FAM*D = family history

Notes:

Dependent variable CHOICE; Log likelihood function -3120.36644; Chi squared [ 56](P= .000)
1992.26762; McFadden Pseudo R-squared .2419856; Inf.Cr.AIC = 6352.7 AIC/N = 1.695

***, **, * ==> Significance at 1%, 5%, 10% level.

*Mixed logit model without interactions*

- The mixed logit model was tested without any interaction terms (**Table 35**
- 247.8 (Test statistic) > 12.592 (critical value)

Table 36). The model fit significantly worse than the chosen model:

- 247.8 (Test statistic) > 12.592 (critical value)
- Log likelihood no interactions: -2894.12350, k = 8
- Log likelihood with interactions for geographical location (included in main manuscript): -2669, k = 23
- Likelihood ratio test: -2 (LL(M1) – LL(M2) ~ X 2 (k2-k1)
- 450.247 (Test statistic) > 24.996 (critical value)

**Table 35. Mixed logit model without interactions**

| CHOICE | Coefficient | Standard Error | z | P-value* | 95% Confidence Interval |
|---|---|---|---|---|---|
| **Random parameters in utility functions** | | | | | |
| CONDS | .26285*** | .07063 | 3.72 | .0002 | .12442 .40128 |
| FALSEP | -.01844*** | .00228 | -8.10 | .0000 | -.02290 -.01398 |
| FALSEN | -.03158*** | .00784 | -4.03 | .0001 | -.04695 -.01621 |
| INCONC | -.03156** | .01555 | -2.03 | .0424 | -.06204 -.00108 |
| SSEX | -.02496 | .03045 | -.82 | .4123 | -.08463 .03471 |
| NUMBER | -.04704 | .07068 | -.67 | .5058 | -.18557 .09150 |
| WWAIT | -.03597*** | .01164 | -3.09 | .0020 | -.05880 -.01315 |
| SCOST | -.00125*** | .9592D-04 | -13.03 | .0000 | -.00144 -.00106 |
| **Nonrandom parameters in utility functions** | | | | | |
| NONE | -2.67348*** | .23532 | -11.36 | .0000 | -3.13470 2.21226 |
| **Distns. of RPs. Std.Devs or limits of triangular** | | | | | |
| NsCONDS | .62847*** | .09797 | 6.41 | .0000 | .43645 .82050 |
| NsFALSEP | .02990*** | .00242 | 12.36 | .0000 | .02516 .03464 |
| NsFALSEN | .06874*** | .01103 | 6.23 | .0000 | .04711 .09036 |

| | | | | | | |
|---|---|---|---|---|---|---|
| NsINCONC | .14225*** | .02006 | 7.09 | .0000 | .10293 | .18158 |
| NsSSEX | .24250*** | .04763 | 5.09 | .0000 | .14915 | .33585 |
| NsNUMBER | .78983*** | .06774 | 11.66 | .0000 | .65706 | .92260 |
| NsWWAIT | .10386*** | .01560 | 6.66 | .0000 | .07329 | .13443 |
| TsSCOST | .00125*** | .9592D-04 | 13.03 | .0000 | .00106 | .00144 |
| CHOICE | Coefficient | Standard Error | z | Prob.\|z\|>Z* | 95% Confidence Interval | |

Abbreviations: CONDS = conditions, FALSEP = false positive, FALSEN = false negative, INCONC = inconclusive, NUMBER = number of tests, WWAIT = waiting time, SCOST = screening cost, NONE = no screening option, Ns = standard deviation of parameter, Ts = triangular distribution
Notes:
***, **, * ==> Significance at 1%, 5%, 10% level.

*Mixed logit model with gender interactions*

The mixed logit model was tested without any interaction terms (**Table 36**). The model fit significantly worse than the chosen model:

- Log likelihood no interactions: -2792.89609, k = 17
- Log likelihood with interactions for geographical location (included in main manuscript): -2669, k = 23
- Likelihood ratio test: -2 (LL(M1) – LL(M2) ~ X 2 (k2-k1)
- 247.8 (Test statistic) > 12.592 (critical value)

**Table 36. Mixed logit model without any interactions**

| CHOICE | Coefficient | Std.error | z | P-value | Lower CI | Upper CI |
|---|---|---|---|---|---|---|
| **Nonrandom parameters in utility functions** | | | | | | |
| COND_B | .09428 | .07282 | 1.29 | .1954 | -.04844 | .23701 |
| COND_F | .40288*** | .08809 | 4.57 | .0000 | .23023 | .57553 |
| FP_B | -.01076*** | .00231 | -4.66 | .0000 | -.01528 | -.00623 |
| FP_F | -.01940*** | .00292 | -6.65 | .0000 | -.02511 | -.01368 |
| FN_B | -.01490** | .00759 | -1.96 | .0495 | -.02977 | -.00003 |
| FN_F | -.03263*** | .01003 | -3.25 | .0011 | -.05229 | -.01297 |
| INCR_B | -.00692 | .01703 | -.41 | .6844 | -.04030 | .02646 |
| INCR_F | -.04153** | .01765 | -2.35 | .0186 | -.07611 | -.00694 |
| SEX_B | -.02055 | .03299 | -.62 | .5333 | -.08521 | .04411 |
| SEX_F | -.01290 | .03969 | -.33 | .7452 | -.09069 | .06489 |
| NTEST_B | .05740 | .05991 | .96 | .3381 | -.06003 | .17483 |
| NTEST_F | .06467 | .06597 | .98 | .3269 | -.06463 | .19397 |

| | | | | | | |
|---|---|---|---|---|---|---|
| WAIT_B | -.02742** | .01123 | -2.44 | .0146 | -.04942 | -.00542 |
| WAIT_F | -.02995** | .01450 | -2.07 | .0389 | -.05838 | -.00152 |
| COST_B | -.00085*** | .00011 | -8.01 | .0000 | -.00106 | -.00064 |
| COST_F | -.00122*** | .00012 | -10.08 | .0000 | -.00146 | -.00099 |
| **Random parameters in utility functions** | | | | | | |
| NONE | -4.22600*** | .33562 | -12.59 | .0000 | -4.88380 | -3.56819 |
| **Distns. of RPs. Std.Devs or limits of triangular** | | | | | | |
| NsCOND_B | .21641 | .19399 | 1.12 | .2646 | -.16379 | .59662 |
| NsCOND_F | .50402*** | .13734 | 3.67 | .0002 | .23485 | .77320 |
| NsFP_B | .02032*** | .00249 | 8.17 | .0000 | .01545 | .02519 |
| NsFP_F | .02837*** | .00326 | 8.71 | .0000 | .02199 | .03476 |
| NsFN_B | .00694 | .03998 | .17 | .8623 | -.07142 | .08529 |
| NsFN_F | .06767*** | .01426 | 4.75 | .0000 | .03973 | .09562 |
| NsINCR_B | .09510*** | .02711 | 3.51 | .0005 | .04196 | .14824 |
| NsINCR_F | .07526** | .03571 | 2.11 | .0351 | .00527 | .14524 |
| NsSEX_B | .12830* | .07288 | 1.76 | .0784 | -.01456 | .27115 |
| NsSEX_F | .25563*** | .05771 | 4.43 | .0000 | .14252 | .36874 |
| NsNTEST_ | .07793 | .27610 | .28 | .7777 | -.46320 | .61907 |
| NsNTEST1 | .02775 | .14834 | .19 | .8516 | -.26298 | .31849 |
| NsWAIT_B | .00207 | .02911 | .07 | .9432 | -.05499 | .05913 |
| NsWAIT_F | .09655*** | .02040 | 4.73 | .0000 | .05657 | .13652 |
| TsCOST_B | .00085*** | .00011 | 8.01 | .0000 | .00064 | .00106 |
| TsCOST_F | .00122*** | .00012 | 10.08 | .0000 | .00099 | .00146 |
| NsNONE | 3.54781*** | .31685 | 11.20 | .0000 | 2.92681 | 4.16882 |

Abbreviations: COND = conditions, FP = false positive, FN = false negative, INCR = inconclusive, NTEST = number of tests, WAIT = waiting time, COST = screening cost, NONE = no screening option, _B = boy, _F = female, Ns = standard deviation of parameter, Ts = triangular distribution
Notes: ***, **, * ==> Significance at 1%, 5%, 10% level.

*Mixed logit model including prenatal screening experience*

The mixed logit model was tested with prenatal screening experience included as main effects and a fixed parameter (**Table 37**). This model includes interaction terms based on remoteness. Prenatal experience was not found to be significant.

**Table 37. Mixed logit model including prenatal screening experience**

| CHOICE | Coefficient | St. Error | z | P-value | Confidence Interval |
|---|---|---|---|---|---|
| **Random parameters in utility functions** | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| COND_R | .31718*** | .09973 | 3.18 | .0015 | .12172 | .51265 |
| COND_M | .14586* | .08654 | 1.69 | .0919 | -.02376 | .31549 |
| FP_R | -.01618*** | .00291 | -5.57 | .0000 | -.02188 | -.01049 |
| FP_M | -.01323*** | .00288 | -4.59 | .0000 | -.01889 | -.00758 |
| FN_R | -.02062** | .01031 | -2.00 | .0455 | -.04082 | -.00041 |
| FN_M | -.02897*** | .00940 | -3.08 | .0021 | -.04740 | -.01053 |
| INCR_R | -.05185*** | .01839 | -2.82 | .0048 | -.08790 | -.01580 |
| INCR_M | .00067 | .02057 | .03 | .9742 | -.03965 | .04098 |
| SEX_R | -.03119 | .03798 | -.82 | .4115 | -.10563 | .04325 |
| SEX_M | -.01353 | .04102 | -.33 | .7415 | -.09393 | .06686 |
| NTEST_R | .02270 | .07575 | .30 | .7644 | -.12577 | .17117 |
| NTEST_M | .06866 | .07729 | .89 | .3744 | -.08284 | .22015 |
| WAIT_R | -.03123** | .01447 | -2.16 | .0308 | -.05959 | -.00288 |
| WAIT_M | -.02358* | .01377 | -1.71 | .0869 | -.05056 | .00341 |
| COST_R | -.00101*** | .7982D-04 | -12.69 | .0000 | -.00117 | -.00086 |
| COST_M | -.00097*** | .7717D-04 | -12.59 | .0000 | -.00112 | -.00082 |
| AGE | -.03711 | .29070 | -.13 | .8984 | -.60687 | .53266 |
| MALE | -.45901 | .31145 | -1.47 | .1405 | -1.06944 | .15142 |
| UNI | -.13626 | .27695 | -.49 | .6227 | -.67906 | .40655 |
| FAM | .56700 | .43861 | 1.29 | .1961 | -.29266 | 1.42666 |
| TERM | -.31241 | .28316 | -1.10 | .2699 | -.86739 | .24257 |
| INCOMEL | .60867 | 1.02872 | .59 | .5541 | -1.40758 | 2.62491 |
| NONE | -3.75051*** | .52721 | -7.11 | .0000 | -4.78382 | -2.71721 |
| **Nonrandom parameters in utility functions** | | | | | | |
| SCREEN | .34261 | .29136 | 1.18 | .2396 | -.22845 | .9136 |
| **Distns. of RPs. Std.Devs or limits of triangular** | | | | | | |
| NsCOND_R | .45998*** | .12658 | 3.63 | .0003 | .21189 | .70808 |
| NsCOND_M | .31264* | .17480 | 1.79 | .0737 | -.02997 | .65525 |
| NsFP_R | .02502*** | .00309 | 8.10 | .0000 | .01897 | .03108 |
| NsFP_M | .02293*** | .00324 | 7.07 | .0000 | .01657 | .02928 |
| NsFN_R | .04654*** | .01386 | 3.36 | .0008 | .01937 | .07370 |
| NsFN_M | .03263 | .02314 | 1.41 | .1584 | -.01271 | .07798 |
| NsINCR_R | .07500** | .03794 | 1.98 | .0481 | .00064 | .14935 |
| NsINCR_M | .09813*** | .03596 | 2.73 | .0064 | .02765 | .16862 |
| NsSEX_R | .14719** | .07064 | 2.08 | .0372 | .00873 | .28565 |
| NsSEX_M | .18995** | .07803 | 2.43 | .0149 | .03701 | .34289 |

| | | | | | |
|---|---|---|---|---|---|
| NsNTEST_ | .04411 | .60784 | .07 | .9421 | -1.14724 1.23546 |
| NsNTEST1 | .06651 | .57070 | .12 | .9072 | -1.05204 1.18506 |
| NsWAIT_R | .04363* | .02508 | 1.74 | .0819 | -.00553 .09280 |
| NsWAIT_M | .05390** | .02624 | 2.05 | .0400 | .00247 .10532 |
| TsCOST_R | .00101*** | .7982D-04 | 12.69 | .0000 | .00086 .00117 |
| TsCOST_M | .00097*** | .7717D-04 | 12.59 | .0000 | .00082 .00112 |
| NsAGE | 1.25259 | 1.83592 | .68 | .4951 | -2.34575 4.85093 |
| NsMALE | 1.98943 | 1.52366 | 1.31 | .1917 | -.99689 4.97575 |
| NsUNI | .57420 | 1.82322 | .31 | .7528 | -2.99924 4.14764 |
| NsFAM | .48214 | 1.98891 | .24 | .8085 | -3.41605 4.38033 |

Abbreviations: COND = conditions, FP = false positive, FN = false negative, INCR = inconclusive, NTEST = number of tests, WAIT = waiting time, COST = screening cost, _R = rural, _M = metropolitan, AGE = age, MALE = male gender, UNI = university education, FAM = family history, TERM = termination attitudes, INCOMEL = income level, NONE = no screening option, SCREEN = screening, Ns = standard deviation of parameter, Ts = triangular distribution
Notes: ***, **, * ==> Significance at 1%, 5%, 10% level.

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# Chapter 6:

# Integrating intermediate outcomes into economic models: A case study using prenatal screening

The research presented in Chapter 2 found that economic models of genetic and genomic testing focus on final health outcomes. The work presented in this chapter explored expanding the models' scope by incorporating intermediate outcomes, using NIPT as a case study. Through a narrative review, the various approaches for integrating stated preference research, particularly DCEs, into health technology assessments were identified. These insights were applied by conducting an economic analysis that demonstrated how including intermediate outcomes derived from a DCE affects economic modelling results and potential funding decisions. This research builds on earlier work by incorporating the WTP estimates from the DCE in Chapter 5 into two economic models developed in Chapter 3. CUA and NMBA were employed to examine how these estimates influenced the models.

The research in this chapter addressed two key challenges. Key challenge (1) Model Structure was addressed by reinforcing the findings of Chapter 3 and demonstrating the considerable influence of differing levels of complexity on modelled results. Key challenge (2) Selection of Outcomes was addressed by demonstrating that both the CUA and NMBA approaches enable estimation of the impact of intermediate outcomes in economic evaluations, offering a more comprehensive assessment of prenatal screening. Of these approaches, CUA provides the more practical option for Australia given current HTA frameworks.

## Abstract

**Background:** There is increasing demand for economic evaluation approaches that incorporate intermediate and process outcomes within genetic and genomic testing. Although discrete choice experiments (DCEs) have been recommended for valuing these outcomes, integrating these values into economic models remains problematic.

**Aims:** (1) To evaluate how integrating willingness to pay (WTP) estimates of intermediate outcomes (derived from a DCE) influences the cost-effectiveness of second-line non-invasive prenatal testing (NIPT) versus combined first trimester screening (cFTS) for detecting Down syndrome; (2) to compare cost-effectiveness results using cost-utility analysis (CUA) and net marginal benefit analysis (NMBA) when incorporating these WTP estimates.

**Methods:** Four analyses were performed evaluating NIPT against cFTS for detecting Down syndrome: CUA with and without intermediate outcomes, and NMBA with and without intermediate outcomes. The base case analysis used a microsimulation with five health states (model M5), and structural uncertainty was explored through the use of a decision tree with three health states (model D3). One-way, two-way, and probabilistic sensitivity analyses were conducted.

**Results:** In model M5, the inclusion of intermediate outcomes caused the CUA incremental cost-effectiveness ratio (ICER) and net marginal benefit (NMB) to become less favourable. In model *D3*, incorporating intermediate outcomes increased the ICER from AUD48,927 to AUD130,043/QALY gained, and caused the NMB to shift from positive (AUD 0.37) to negative (-1.49), arguing against public funding for NIPT.

**Conclusions:** These results highlight the considerable impact intermediate outcomes can have on cost-effectiveness results of NIPT. The results and potential policy implications were consistent across the CUA and NMBA. Due to the current health technology assessment framework within Australia, CUA may be more practical to implement than NMBA.

## Introduction

The complexity of genetic and genomic testing challenges existing methods for economic evaluations. Due to the possible scope of testing, the hereditary nature of many conditions, and the incomplete understanding of the genome, these tests can generate a wide range of outcomes that extend beyond clinically actionable diagnoses. These outcomes may include non-clinical outcomes (e.g., the value of knowing from receiving a diagnosis that does not alter management of the condition) as well as intermediate and process outcomes. Intermediate outcomes can include the psychological effects of receiving a false positive or uncertain result, while process outcomes can involve factors such as wait times, or the inconveniences associated with undergoing a test. Stated preference methods, particularly discrete choice experiments (DCEs), have been recommended to value the full range of outcomes linked to genetic and genomic testing.[1] However, incorporating these values into economic models and/or public funding decisions remains a significant challenge.[2-5]

This challenge is part of a wider discussion on how stated preference research could or should be incorporated into health technology assessments. The literature within this area focuses on two questions: (1) which factors should be valued? (i.e., health outcomes with or without process or intermediate outcomes) and (2) whose preferences should be valued? (i.e., patient or public preferences). These questions stem from the theoretical debate between welfarist and extra-welfarist approaches.[6, 7] The welfarist perspective advocates for incorporating all consequences, reflecting the values of those affected (i.e., patients), while the extra-welfarist approach considers only health outcomes, reflecting societal values (i.e., the public). As a result, the questions of which factors should be valued and whose preferences should be valued often overlap in the literature. Several studies discuss the use of "quantitative preference" or "patient preference" data (i.e., stated preference methods such as DCEs) to capture process or intermediate outcomes from the patient perspective.[8, 9] However, stated preference methods can also be applied to capture these outcomes from the general population perspective. The ISPOR Special Task Force recognises these as distinct issues that should be addressed separately, and this chapter focuses on the former consistent with the extra-welfarist approach recommended by HTA bodies in Australia.[10, 11]

This article has two linked components: Part A describes a narrative review of methods for incorporating stated preference research into HTA, identifying key approaches for further investigation. Part B reports on the application of these insights through an evaluation that incorporates stated preferences research for intermediate outcomes into economic models.

## Part A: Narrative review

### *Methods*

We aimed to explore how stated preference research could be incorporated into health technology assessments. We conducted a narrative review to identify the range of approaches proposed within the literature, focusing on question (1): which factors should be valued? However, we also present approaches that address question (2): whose preferences should be valued? due to the interconnected way they have been presented in the literature, whilst attempting to differentiate between them. We then chose the most suitable approaches to explore in our case study of prenatal screening and for our broader research goals of incorporating intermediate outcomes into economic models. Additional details of the review, including the databases and search terms, can be found in the Supplementary materials (**Error! Reference source not found.**).

### *Results*

The following section summari*s*es our findings and the key approaches identified in our review. Full details of the included studies are available in the Supplementary materials (**Table 46**)

#### *Overview of identified approaches*

A previous critical review identified several approaches to incorporate stated preference research into HTAs: trade-off assessment, preference share, estimation of QALY gains, construction of efficiency frontiers, cost-benefit analysis using willingness to pay (WTP) or willingness to accept (WTA) estimates, and multicriteria decision analysis (**Table 38**).[12] We expanded this list to include cost-utility analysis using WTP estimates[13], cost-consequence analysis[14, 15], modified-net marginal benefit analysis, and a stand-alone supplementary analysis.[16, 17] We then categorised these approaches into groups based on whether they allow for the direct incorporation of stated preference research into economic models, or if they serve as indirect or supplementary methods. Additionally, we considered whether each approach captures process or intermediate outcomes or has other applications for stated preference research. Further, we included additional and more recent examples of how these latter approaches have been applied compared to those presented in the critical review.

**Table 38. Overview of methods to incorporate stated preference research into health technology assessments**

| Approaches | Description | Examples |
|---|---|---|
| **Direct incorporation of stated preference results into economic models** | | |
| Cost–benefit analysis using WTP or WTA estimates | Including a cost attribute in a stated preference study allows WTP or WTA for improvements in benefits (or reductions in risks) to be calculated. These estimates can be used to value process or intermediate outcomes within a cost-benefit analysis and allow for incorporation of patient preferences. | Regier 2010,[18] Tinelli 2015,[19] Costa 2023,[20] Goranitis 2022,[21] Jayasinghe 2021,[22] Wu 2022[23] |
| Net marginal benefit analysis (NMBA) using WTP or WTA estimates | Including a cost attribute in a stated preference study allows WTP (or WTA) for improvements in benefits (or reductions in risks) to be calculated. These estimates can be used to value process or intermediate outcomes within a NMBA and allow for incorporation of patient preferences. | Not identified within the literature. |
| Cost-utility analysis using WTP or WTA estimates | Including a cost attribute in a stated preference study allows WTP (or WTA) for improvements in benefits (or reductions in risks) to be calculated. These estimates can be attributed as a cost (rather than an outcome) to value process or intermediate outcomes within a cost-utility analysis and allow for incorporation of patient preferences. | Suggested within the literature, but no applied examples could be identified.[13] |
| Cost-consequence analysis | This method involves evaluating the costs and consequences of a treatment or intervention without combining them into a single metric. Process or intermediate outcomes can be presented in natural units. This approach also allows for incorporation of patient preferences. | Suggested within the literature, but no applied examples could be identified.[14, 15] |
| Quality-adjusted survival equivalents (QASE) | The QASE approach is based on DCEs that included both process/intermediate and survival attributes. Survival equivalents for changes in process/intermediate attributes can then be estimated through the marginal utility of survival and the process/intermediate attribute. This approach also allows for incorporation of patient preferences. | Marsh 2024[24] |
| Estimation of QALY gains using preference studies | Stated preference methods (time trade-off studies or standard gamble, where there is a trade-off with death) can be used to estimate changes in utilities associated with process or intermediate outcomes. These methods can be used with a patient population. | Burr 2007[25] Kaimal 2015,[26] Wang 2012,[27] Guzauskas 2022[28] |
| Other uses of stated preference results (i.e. not specific to enabling process or intermediate outcomes to be captured) | | |
| Uptake rates (preference share) | Preference data can be used to predict intervention uptake, which is used to parameterise economic models. This approach can allow for the incorporation of patient preferences. | Govathson 2023[29] |

| Indirect or supplementary (stand-alone) approaches to economic models | | |
|---|---|---|
| Contextual or supplementary information | Preference data is included as contextual or supplementary information with the public funding assessment. This can be patient preferences and/or process or intermediate outcomes. | Section 3 & Appendix 6 of PBAC Guidelines[17]; TG29 and Appendix 10 of the MSAC Guidelines[16] |
| Multicriteria decision analysis (MCDA) | Preference data are used to weight criteria relevant to HTA, including health gain (e.g., QALYs), process or intermediate outcomes, cost, and disease severity. The MCDA generates an assessment of the overall value of a treatment. This can include outcomes from the patient perspective. | Zamora 2021[30] |
| Trade-off assessment | Preference data can be used to understand trade-offs between the differences in available technologies. Two applications of trade-off assessment include endpoint selection (health and/or process or intermediate outcomes), in which preference data is used to understand the relative importance of endpoints, either clinician or patient-reported, and clinical benefit rating, in which the relative value of benefits can be assessed, such as minimum required benefit. This is usually limited to patient perspective rather than public perspective and is conducted alongside clinical trials. | Palatano 2007[31], Ontario Health 2020[32] |
| Construction of efficiency frontiers | Preference data is collected for indication-specific treatment attributes. These preferences are used to translate the performance of treatments on these attributes into an overall benefit score. Plotting treatment scores and costs allows the construction of an efficiency frontier. This can allow for process or intermediate outcomes and patient perspectives. | Bains 2021[33] |

Abbreviations: DCE, discrete choice experiment; HTA, health technology assessment; MCDA, Multicriteria decision analysis; MSAC, Medical Services Advisory Committee; NMBA, net marginal benefit analysis; PBAC, Pharmaceutical Benefit Advisory Committee; QALY, quality adjusted life year; QASE, Quality-adjusted survival equivalents; WTA, willingness to accept; WTP, willingness to pay.

*Guidelines and recommendations (process or intermediate outcomes)*

Globally, there is growing interest among HTA bodies in the use of stated preference research for valuing process or intermediate outcomes, with a particular focus on DCEs. Recommendations vary widely, from formal guidelines advocating for the inclusion of process or intermediate outcomes (as seen in the Netherlands)[34] to no mention of such outcomes (as seen in France,[35, 36] Germany,[37] and Ireland[38]) (see **Table 39**).

**Table 39. HTA guidelines from different countries, highlighting recommended preferences, perspectives and consideration of process or intermediate outcomes.**

| | Australia | France | Germany | Netherlands | England | Ireland | Canada |
|---|---|---|---|---|---|---|---|
| Preferences | Public | Public | Patients | Public | Public | Public | Public |
| Evaluation perspective (base-case)* | Healthcare system | All funders | Statutory health insurance | Societal | National Health Service and Personal Social Services | Healthcare payer | Healthcare system |
| Intermediate and/or process outcomes | Supplementary | No mention | No mention | Include | Considered when ICER falls within certain values | No mention | May be considered |

Abbreviations: HTA, health technology assessment; ICER, incremental cost-effectiveness ratio.
Notes: Selected examples of countries with accessible guidelines in English.
* The wording for the evaluation perspective has been taken directly from each country's guidelines.

Further differences emerge among countries that include process or intermediate outcomes within their guidelines. In Australia, the Medical Services Advisory Committee (MSAC) and Pharmaceutical Benefit Advisory Committee recommend using supplementary methods, such as DCEs and conjoint analysis, to estimate the monetary (or other) value of interventions that provide direct process or intermediate outcomes.[16, 17] If there is no substantial impact on clinically actionable outcomes, the WTP for process or intermediate outcomes can be integrated into a supplementary cost-benefit analysis (CBA). The Netherlands acknowledges interventions may provide process or intermediate benefits that should be included in economic evaluations, and recommends valuing these outcomes using DCEs or MCDA.[34] It does not provide specific recommendations on how to incorporate DCE results into evaluations, although a CBA is mentioned as a possible approach. The National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK) will specifically consider process or intermediate outcomes and uncaptured benefits when the incremental cost-effectiveness ratio (ICER), without the inclusion of process or intermediate outcomes, falls between GBP20,000 and GBP30,000 per QALY, although the method of doing so is not clearly stated.[39] NICE does not recommend the incorporation of patient preference data (such as DCEs) directly into economic models, because it contends that preferences should reflect the values of the general population rather than patients, because taxpayers fund healthcare in the UK. This justification is related to the perspective taken (patient vs general population), rather than whether intermediate or process outcomes should be directly incorporated into economic models. Canada's Drug Agency (previously Canadian Agency for Drugs and Technologies in Health) suggests exploring process or intermediate outcomes using a cost-consequence analysis or within a scenario analysis using a CBA.[14]

A recent survey of the perspectives of HTA representatives across Europe, North America, Australia, and Asia found that most representatives reported that preference data is considered as part of the evidence for decision-making, but many noted the lack of formal guidance.[8] The main barriers to incorporating this evidence in decisions were reported to be resource constraints (time, money and other resources) and a lack of clarity on the impact of preference data, rather than the view that

process or intermediate outcomes are not important. These perspectives underscore the relevance of the ISPOR Special Task Force's report, which expands the definition of value in health economics beyond just clinically actionable outcomes.[10] The report promotes research into incorporating additional elements of value into cost-utility analysis (CUA) or cost-effectiveness analysis (CEA).

*Applied examples*

The integration of process or intermediate outcomes into economic models remains poorly examined, with few applied examples exploring the proposed approaches. Tinelli et al.[19] incorporate process and intermediate outcomes through using WTP estimates from a DCE into a CBA, and compare the results with those of a CUA (without process or intermediate outcomes). Their case study of a pharmacy service found no differences between intervention and control groups in the CUA, while the CBA incorporating process or intermediate outcomes favoured the intervention. Costa et al.[20] integrated WTA values for process outcomes from a DCE into a CBA evaluating collaborative intervention between pharmacies and primary care. Their findings revealed wait times had a large influence on the results. We identified four studies within the field of genomics that incorporated DCE results as WTP estimates in CBAs.[18,21-23] Three other studies within genomics relied on time trade-off studies to generate utility estimates for intermediate or process outcomes.[26-28] Since these outcomes were traded off with death, there was limited ability to capture their impacts. Recently, Marsh et al.[24] took a similar approach using DCEs, estimating the value of process outcomes in terms of QASE (Quality-Adjusted Survival Equivalents) to be used within a CUA, based on a NICE submission for Fabry disease treatment. The QASE was based on DCEs that included both mode of administration and survival as attributes. Survival equivalents for changes in mode of administration were estimated using the marginal utility of survival and mode of administration. We found no studies that incorporated process or intermediate outcomes using WTP estimates into a cost-utility analysis, although it has been suggested in the literature, without discussion of its justification or feasibility.[13] This approach values intermediate outcomes differently, by trading them off against cost rather than death, which may better capture their impact. We did not identify any applied examples of cost-

consequence analyses using stated preference results, although Canada's Drug Agency and the UK's National Institute for Health Research have recommended this approach.[14, 15]

## Part B: Economic evaluation

### *Rationale for current study*

Based on the results of the narrative review in Part A, we chose to explore the integration of WTP estimates within both a NMBA and CUA. When choosing which approaches to explore, we focused on those that allow process or intermediate outcomes to be incorporated directly into economic models.

We initially intended to explore a CBA because it is the conventional method when using WTP estimates,[40] frequently cited in HTA guidelines for its broader perspective,[16, 17] and the literature offers few examples of incorporating process or intermediate outcomes into a CBA. However, a CBA would have required monetising outcomes using either the human capital approach or estimating the WTP to avoid the birth of a child with Down syndrome. Due to a lack of evidence and the practical and ethical challenges of obtaining relevant data (described further in the Methods section), we opted against pursuing CBA.

Instead, we explored a NMBA, which values QALYs using a predefined monetary threshold, avoiding the complexities of direct monetisation. The CUA approach incorporating WTP estimates has been proposed as a theoretical framework in the literature, but its practical application remains unresearched. Given the absence of a standard QALY threshold in Australia to guide the NMBA approach, the CUA approach warrants further investigation.

We chose not to explore the use of QASE within a CUA, because this method requires the inclusion of survival in the DCE, which is complicated in the context of prenatal screening where termination is a choice. We similarly chose not to explore the incorporation of utilities generated using a standard gamble or time trade-off study into a CUA due to the trade-off against death. Further, the identified examples in Part A underlined this methodology's inability to appropriately capture the impacts of intermediate and process outcomes.[26] Finally, we chose not to use a cost-consequence analysis because this method is used infrequently in Australian HTAs.

We aimed to:

(1) Evaluate how integrating WTP estimates for intermediate outcomes, derived from a DCE, influences cost-effectiveness results in economic evaluations of second-line NIPT versus cFTS for the detection of Down syndrome (T21).

(2) Compare the cost-effectiveness of two approaches (CUA and NMBA) to integrating WTP estimates for intermediate outcomes into economic evaluations of second-line NIPT versus cFTS for the detection of Down syndrome (T21).

## *Methods*

### *Key model components*

The work in this article builds upon the models described in a previous publication.[41] Here, we present the key components of these models.

#### *Intervention and comparator*

We defined the intervention as second-line NIPT. cFTS results were classified as high risk (risk score >1:10), intermediate risk (risk score >1:300), or low risk (risk score <1:300). It was assumed that women with a high-risk result are offered invasive diagnostic testing, women with an intermediate risk result are offered NIPT, and women with a low-risk result are not offered further testing. Women with a positive NIPT result are subsequently offered an invasive test. We defined the comparator as conventional screening, in which women with a cFTS test risk of >1:300 are offered invasive diagnostic testing. The core components of the models are shown in **Table 40**.

**Table 40. Core components of models evaluating NIPT against cFTS.**

| Component | | Justification |
|---|---|---|
| **Population** | All singleton pregnancies regardless of trisomy risk. | Simplification as different data are required for multiple pregnancies and these data are less reliable.[42] |
| **Setting** | Australia | Application of methods is intended for the Australian decision-making context. |
| **Timing** | All pregnant women enter at first trimester only | Recommended when screening for Down Syndrome is conducted. |
| **Intervention** | cFTS followed by NIPT in cFTS intermediate risk pregnancies and invasive testing in cFTS high-risk pregnancies | Second-line testing is the most likely option to be funded in Australia. |
| **Comparator** | cFTS with no NIPT and invasive testing in intermediate or high-risk pregnancies. | Current publicly funded testing in Australia. We have not included private NIPT use due to the lack of reliable data, and because we are interested in the perspective of the healthcare funder and policy implications. |
| **cFTS intermediate risk cut off** | cFTS trisomy risk score of >1:300 | Based on clinical advice and local hospital guidelines.[43] |
| **cFTS high risk cut off** | cFTS trisomy risk score of >1:10 | Based on clinical advice this value ranges from 1/10 to 1/100. 1/10 is the conservative approach. |
| **Perspective** | Healthcare funder | Recommended in local HTA guidelines.[44] We are interested in how modelling informs decision-making. |
| **Types of aneuploidies** | T21 | Simplification. T21 is being used as the case-study, but there will be implications for other uses of NIPT. |
| **Time horizon** | Pregnancy duration | Simplification that avoids ethical considerations that are beyond the scope of this study, and this is the duration used by MSAC.[45] |
| **Discount rate** | None | Time horizon is less than one year. |
| **Currency** | AUD | AUD are presented as the model is set within the Australian context. |
| **Year of analysis** | 2024 | Present context. |

Abbreviations: AUD, Australian Dollar; cFTS, combined first trimester screening; HTA, health technology assessment; MSAC, Medical Services Advisory Committee; NIPT, non-invasive prenatal testing; T21, Trisomy 21.

*Model structure*

In a previous publication,[41] we described four demonstration models with varying structures in TreeAge™, and used them to compare three versus five health states and a cohort-based decision tree approach versus microsimulation (reflecting the decision to incorporate risks based on maternal age). Based on the findings, the microsimulation with five health states was deemed the most appropriate representation of the true pathway, so we selected this model (M5) to expand for this analysis. A diagram of the model structure can be found within the Supplementary materials [Chapter 3, Section H].

*Analysis methods*

The following analyses were conducted.

**(**1) Cost-utility analyses

(a) Without intermediate outcomes: standard analysis comparing the costs and benefits in terms of QALYs. This is the same analysis as presented in Salisbury et al.[46]

(b) With intermediate outcomes: the WTP estimates to avoid a false positive and WTP estimates to avoid an inconclusive result (both obtained from the results of the DCE described in Salisbury et al.[46]) were input as **an increase in the cost** at the relevant stage within the model.

The results are presented as the ICER, based on the following formula.

$$\frac{\text{Cost (NIPT)} - \text{Cost (cFTS)}}{\text{QALYs (NIPT)} - \text{QALYS (cFTS)}}$$

(2) Net marginal benefit analysis

(a) Without intermediate outcomes: standard analysis comparing the costs and benefits in terms of monetary units.

(B) With intermediate outcomes: the WTP estimates to avoid a false positive rate, and WTP estimates to avoid an inconclusive result (from Salisbury et al.[46]) were input as a **decrement in the benefit** at the relevant stage within the model

The results are presented as the net marginal benefit (NMB), formula as follows:

[Benefits (NIPT) – Benefits (cFTS)] - [Costs (NIPT) – Costs (cFTS)]

### *Costs and outcome inputs*

#### *Cost-utility and net marginal benefit analysis*

Clinical parameters were obtained from a large, randomised control trial[47] and costs were obtained from the Australian Medical Benefits Schedule (see Supplementary Materials, [Chapter 3, Section B]). In this case study, we aimed to capture the psychological impacts of receiving a false positive or inconclusive result (both intermediate events). These impacts were captured indirectly by quantifying the WTP to avoid a false positive and the WTP to avoid an inconclusive result, which are referred to as intermediate outcomes from here on. We derived WTP estimates from the DCE in our previous publication,[46] and present them in **Table 41**. These values represent the WTP to avoid a 1% increase in the false positive rate and 1% increase in the inconclusive rate. For the CUA, the cost associated with the relevant health states, such as receiving a positive result for an unaffected fetus, was calculated by multiplying the WTP to avoid a 1% increase in the false positive rate by 100, reflecting the preference to avoid this state. For the NMBA, the "benefit" associated with a false or inconclusive result was calculated as the negative of this value. Both analyses assumed a linear WTP, consistent with the approach taken by the CBAs that incorporate WTP estimates derived from DCEs identified in the narrative review.[21, 23]

**Table 41. Willingness to pay estimates used to value intermediate outcomes, derived from a discrete choice experiment (Salisbury et al.[46])**

| | Metropolitan | Rural | Weighted* |
|---|---|---|---|
| Avoid a 1% increase in the false positive rate | $13 | $16 | $14 |
| Avoid a 1% increase in the inconclusive rate | **$0 | $51 | $14 |

* The results were weighted by the ratio of metropolitan to non-metropolitan residents in Australia, as per Australian Institute of Health and Welfare data (June 2022).[48]
** This result was not significant, thus a value of $0 was used.

There were no time dependencies within the models, and as a result we did not incorporate the WTP to avoid waiting for the results (considered a process outcome), also derived from the DCE

in our previous publication.[46] The decrement in benefit or increase in cost associated with a false positive was applied each time a false positive result was received (up to twice for second-line NIPT), reflecting the increased psychological burden of multiple false positives, as identified in the focus group discussions in our previous publication.[49]

*Cost-utility analysis*

A comprehensive supplementary literature review was conducted to identify appropriate utility weights (from the mother's perspective). Details can be found within the Supplementary Materials [Chapter 3, Section C]. Based on this review, we used the utilities presented by Kupperman 2016.[50]

*Net marginal benefit analysis*

To monetise the outcomes, we multiplied the utilities for the relevant health state by the monetary value of a QALY. Because there is no consensus on the value of a QALY, we explored values ranging from AUD28,000 to AUD65,000, with the justification for each value presented in **Table 42**. We note that other studies have used and recommended the value of a statistical life (AUD235,000 in Australia[40]) to monetise the value of a QALY.[51, 52] However, this value is not in line with the empirical evidence about reimbursement decisions in Australia.[53]

Alternative methods for monetising the outcomes were considered. One CBA of NIPT was identified in our systematic review of economic models of NIPT.[54] This CBA valued outcomes using the WTP to avoid a birth of a child with Down syndrome (mother's perspective). However, because this study was conducted in Thailand, the WTP estimates were not applicable to our context. No relevant WTP estimates were identified within the literature. Other CBAs use the "human capital approach" by considering lifetime earnings or productivity.[55] However, applying similar methods to prenatal screening is ethically and practically complex due to the need to place a value on terminations and the birth of a child with disability

**Table 42. Values of a QALY used in the analysis**

| | Value | Justification |
|---|---|---|
| Low value | AUD28,000 | Edney et al.[56] derived this value by estimating the increase in government health spending across all sectors and the resulting QALY gained per capita from that increased expenditure in Australia.<br>All applications for genetic and genomic tests related to heritable conditions submitted to the Australian MSAC that were below this value received approval.[57] |
| Middle value | AUD50,000 | A commonly cited reference threshold, though it is acknowledged that it does not accurately reflect decision-making in Australia or overseas.[58] |
| High value | AUD65,000 | National lung cancer screening program was found to be cost-effective at AUD65,000/QALY.[53] This case study was selected to guide the value due to its relevance within a screening context and being recent. Note that in a previous consideration of this screening program three months earlier, MSAC considered an ICER of AUD83,545 to be too high.[59]<br>The value of AUD65,000 is also in line with the upper value presented by Huang et al,[60] who found an Australian WTP for a QALY between AUD 42,000-67,000 using a longitudinal survey. |

Abbreviations: AUD, Australian Dollar; ICER, Incremental Cost-Effectiveness Ratio; MSAC, Medical Services Advisory Committee; QALY, Quality-Adjusted Life Year; WTP, Willingness To Pay.

*Scenario analysis*

To explore the impact of structural uncertainty, we conducted a scenario analysis using a decision tree with three health states, labelled Model D3 (developed in our previous publication[41]).

*Sensitivity analysis*

We conducted one-way sensitivity analyses on the parameters identified as most uncertain in our previous publication[41]: uptake of NIPT and diagnostic testing, and the WTP estimates. A multi-way sensitivity analysis was performed on the WTP estimates to examine potential interactions between these related parameters.

### *Results*

An overview of the impacts of including intermediate outcomes within the economic model of NIPT against cFTS is presented in **Table 43**, with further details on the results discussed below. The complete set of results, including costs, outcomes, and incremental findings, can be found in the Supplementary Materials (**Table 47**, **Table 48**).

#### *Base case analysis*

In the CUA without intermediate outcomes, the ICER was negative and NIPT was dominated (more costly and less effective, -AUD22,720/QALY gained). Including the intermediate outcomes caused the ICER to become less favourable (-AUD40,244/QALY gained).

In the NMBA without intermediate outcomes, NIPT was dominated and the NMB was negative across the considered values of a QALY, ranging from -AUD3 to -AUD5. Including the intermediate outcomes caused the NMB to become more negative across the considered values of a QALY, ranging from -AUD5 to -AUD7.

#### *Scenario analysis*

Exploring the impact of model structure, in the CUA without intermediate outcomes, the ICER was AUD48,927/QALY, suggesting NIPT would likely be considered to have acceptable cost-effectiveness in the context of a public funding decision. Including the intermediate outcomes caused the ICER to increase to AUD130,043/QALY gained, making NIPT less cost-effective and less likely to be considered as cost-effective.

In the NMBA, using a QALY value of AUD28,000 and without intermediate outcomes, the NMB was negative (-AUD$0.488). Including intermediate outcomes caused the NMB to become more negative (-AUD2.36). Using a QALY value of AUD50,000 or AUD65,000 resulted in a positive NMB when intermediate outcomes were not considered (AUD0.025 and AUD0.37 respectively), suggesting NIPT would likely be considered cost-effective. Including intermediate outcomes caused the NMB to become negative (-AUD1.85 and -AUD1.49 respectively), suggesting NIPT would be unlikely to be considered cost-effective.

**Table 43. Overview of the impact of including intermediate impacts on the cost-effectiveness of NIPT and potential policy implications.**

| **Impact of including intermediate outcomes on the cost-effectiveness of NIPT** | | | | | |
|---|---|---|---|---|---|
| Analysis | | CUA | NMBA | | |
| | | | 1 QALY = AUD28,000 | 1 QALY = AUD50,000 | 1 QALY = AUD65,000 |
| Base-case (Model M5) | Without intermediate outcomes | NIPT is *more* expensive and *less* effective | NMB: - AUD 3.1 | NMB: - AUD4.34 | NMB: -AUD5.18 |
| | With intermediate outcomes | NIPT is *more* expensive and *less* effective | NMB: - AUD 4.9 | NMB: -AUD6.12 | NMB: - AUD 7.00 |
| Alternative scenario (Model D3) | Without intermediate outcomes | AUD48,927 per QALY gained | NMB: - AUD 0.49 | NMB: AUD0.03 | NMB: AUD0.38 |
| | With intermediate outcomes | AUD130,043 per QALY gained | NMB: - AUD 2.36 | NMB: - AUD 1.85 | NMB: - AUD 1.49 |

Abbreviations: AUD, Australian Dollar; CUA, cost-utility analysis; D3, decision tree with 3 health states; ICER, incremental cost-effectiveness ratio; M5, microsimulation with 5 health states; NIPT, non-invasive prenatal testing; NMB, net monetary benefit; NMBA, net-marginal beenfit analysis; QALY, quality-adjusted life year; T21, Trisomy 21.

Notes:

- This table compares the analysis of second line NIPT and combined first trimester screening for the detection of T21 without intermediate impacts, with the same analysis including intermediate impacts.
- Grey shading indicates no substantial change in cost-effectiveness due to the inclusion of intermediate impacts (e.g., the ICER or NMB remains negative). A substanital change is defined as one which is likely to influence policy decisions. Orange shading indicates a shift in cost-effectiveness from more favourable (and more likely to be funded) to less favourable (and less likely to be funded).
- Positive ICER results are quantified, while negative ICER results are described (e.g., “less expensive and less effective”).

*Sensitivity analysis*

In the CUA, adjusting the WTP values for avoiding a false positive and/or the inconclusive rate caused the ICER to vary from -AUD135,896 to -AUD17,526/QALY gained (**Table 44**). In the NMBA (where 1 QALY = AUD50,000), adjusting the WTP values for avoiding a false positive and/or the inconclusive rate caused the NMB to vary from -AUD10.3 to -AUD3.8. Additional sensitivity analyses are provided in the Supplementary materials (**Table 49**).

**Table 44. Sensitivity analysis for willingness to pay estimates for intermediate outcomes for Model M5 (microsimulation, 5 health states)**

| Variable | Current value (AUD 2024) | Range in sensitivity analysis (AUD 2024) | Incremental results (ICER or NMB) (AUD 2024) |
|---|---|---|---|
| **Cost-utility analyses** | | | |
| WTP to avoid a 1% increase in the false positive rate | $14 | $7 to $21 | ICER: -$50,325 to -$49,904/QALY gained |
| WTP to avoid a 1% increase in the inconclusive rate | $14 | $0 to $51 | ICER: -$135,686 to -$17,367/QALY gained |
| Two- way analyses | NR | NR | ICER: -$135,896 to -$17,526/QALY gained |
| **Net marginal benefit analysis (1 QALY = $50,000)** | | | |
| WTP to avoid a 1% increase in the false positive rate | $14 | $7 to $21 | NMB: -5.6 to -5.5 |
| WTP to avoid a 1% increase in the inconclusive rate | $14 | $0 to $51 | NMB: -10 to -4 |
| Two- way analyses | NR | NR | NMB: -10.3 to -3.8 |

Abbreviations: AUD, Australian dollars; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; NR, not relevant; QALY, quality-adjusted life year; WTP, willingness to pay.

### *Discussion*

We explored the practical application of incorporating intermediate outcomes into economic evaluations of genetic and genomic testing, using NIPT as a case study. Depending on the model structure, the inclusion of intermediate outcomes had varying probable effects, ranging from minimal impact on policy decisions to shifting NIPT from being considered for funding to being unlikely to be funded. As expected, these conclusions were consistent whether using the net-marginal benefit or cost-utility approach. Both represent possible approaches for considering intermediate outcomes, with distinct advantages and limitations.

Our study demonstrates that incorporating intermediate outcomes into economic evaluations can substantially alter model findings, depending on the context. In Model M5, although intermediate outcomes worsened cost-effectiveness, their inclusion was unlikely to influence policy decisions. In Model D3, the inclusion of intermediate outcomes substantially worsened the cost-effectiveness of NIPT, arguing against funding. These findings indicate intermediate outcomes disfavour second-line NIPT. This is primarily because both pathways result in the same number of false positives from cFTS, and second-line NIPT introduces further false positives. Additionally, NIPT has a test inconclusive rate of approximately three per cent requiring repeat testing, while cFTS generally provides a risk score for all patients.[47] We would expect the inclusion of intermediate outcomes to have differing impacts based on the clinical application of NIPT. For instance, in the evaluation of first-line NIPT against cFTS for the detection of Down syndrome, we would expect including intermediate outcomes to favour NIPT due to its lower false positive rate. Conversely, when evaluating expanded NIPT, which tests for a broader range of conditions and has a higher false positive rate (up to 55%),[61] intermediate outcomes are likely to disfavour expanded NIPT and have a greater impact on model findings. Within the broader literature, the inclusion of intermediate outcomes was found to drive cost-effectiveness results when evaluating pharmaceutical treatments if their clinical effectiveness was comparable.[19, 20] In genomic testing, intermediate outcomes can influence the assessment of cost-effectiveness substantially due to the potential for multiple non-specific and uncertain findings.

Incorporating intermediate outcomes into either a CUA or a NMBA is a viable approach, although each method raises theoretical economic considerations. While these methods build on the CUA framework, they expand the definition of value beyond its conventional scope (i.e. QALYs) and diverge from the extra-welfarist perspective. However, they do not fully align with a welfarist approach either - otherwise, we would have adopted a CBA to incorporate a broader range of societal outcomes. An opposing view suggests that people consider intermediate health states, by influencing psychological outcomes, to be direct health outcomes.[62] Similarly, some argue that process outcomes can affect uptake and, ultimately, health outcomes. Under this interpretation, both approaches align more closely with extra-welfarist perspective and support HTA objectives. These approaches accept the current assumptions underlying utilities and QALYS, although countries such as Germany are critical of these assumptions.[37]

Moving beyond the question of whether intermediate outcomes should be included in economic evaluations, a key issue is how to capture their value. A previous study on prenatal screening has relied on a time trade off study,[26] which reports only minor utility decrements for these outcomes.[50] However, these findings don't align with the qualitative literature. Our study employs WTP estimates derived from a DCE**,** which we demonstrate can influence modelled results and likely funding decisions. In this framework, individuals make trade-offs between intermediate outcomes, cost, and other relevant attributes. The WTP estimates thus reflect individuals' out-of-pocket expenses rather than the opportunity cost of public expenditure. These estimates may not align with what policymakers are willing to pay on behalf of the public**.** Moreover, the WTP estimates depend on the attributes included in the DCE. These attributes can vary within and across contexts,[63, 64] potentially limiting the generalisability of the results and their applicability in public funding decisions.

Further methodological concerns arise separately in both the CUA and NMBA. In the CUA, intermediate outcomes were monetised and included in the cost side of the equation, which diverges from the standard principle in health economics of keeping costs and outcomes separate.[62] This divergence can lead to two issues: (1) confusion when interpreting the results (i.e., when intermediate outcomes are included incremental costs increase, but this reflects a decrease in incremental benefits),

and (2) increased risk of "double counting" (i.e., incorporating intermediate outcomes on the cost side of a CUA, when these impacts may already be captured within the QALY measure). However, these issues could be minimised through transparent methods and thorough documentation of the costs and benefits.

Building on the CUA approach, the NMBA introduces an additional layer of uncertainty by monetising QALYs. In practice, WTP estimates for final health outcomes are rarely available for the relevant context, making it more feasible to convert utility values (more commonly available) into monetary terms. However, despite recent efforts, there is no consensus on the monetary value of a QALY in Australia.[56, 60] Sectors outside of healthcare often use the value of a statistical life year (VSLY), which the Australian government sets at $235,000,[40] although other values have been suggested.[65] The VSLY is derived from a review of international WTP studies, including stated preference research.[66] This value may be more methodologically aligned with the WTP approach used in this study, as our QALY values reflect reimbursement decisions and the opportunity cost of public funding. However, the review is dated, relying on studies from 1991 to 2005, and lacks Australian research. Given the VSLY substantially exceeds the values used in Australian healthcare reimbursement decisions,[53] its application in this context seems inappropriate.

To our knowledge, this is the first study to explore the incorporation of DCE results into the cost side of a CUA, and to compare this approach with a NMBA. Both approaches enable quantification of how intermediate outcomes affect cost-effectiveness, which has been noted as a key barrier to their consideration in decision-making.[8] Within Australia, these approaches represent only a small deviation from the status quo, making them more feasible for integration into existing decision-making frameworks, with the CUA being the more practical option. This approach offers a pragmatic response to the complex challenges that genomic testing presents to HTA bodies. Nonetheless, concerns remain regarding the underlying theoretical framework (welfarist vs. extra-welfarist) and the methodological choices for valuing outcomes (individual WTP vs. societal or decision-maker estimates). We recommend further research to examine these issues, whilst considering whether the impact on results justifies the adoption of more complex or resource-intensive approaches -

particularly in the context of rapidly evolving genomic technologies. We also encourage researchers to explore how these methods can be applied in countries with predominantly publicly funded health systems (e.g., the UK and Denmark), and to assess the acceptability of these approaches among decision-makers.

*Limitations*

This study focused on which factors should be valued in economic evaluations, rather than whose preferences should be considered. Australian HTA guidelines recommend the use of general population preferences, in line with an extra-welfarist perspective.[16, 17] However, our study used WTP estimates derived from a more targeted population, the general public with an interest in prenatal screening. To account for different preferences, one-way and two-way sensitivity analyses were conducted, revealing that the model findings were sensitive to the value of the WTP estimates. Furthermore, the impacts of intermediate outcomes were reliant on the validity of the WTP estimates, which we also attempted to capture through sensitivity analyses. While there is evidence regarding the psychological impact of undergoing a diagnostic test,[67] we did not identify any WTP estimates that reflect this intermediate state, and it was therefore not included in the model. The inclusion of such outcomes would favour NIPT. Lastly, our study focused on two potential approaches for incorporating intermediate outcomes into decision-making, but a range of other approaches could be considered. We conducted a narrative review to identify the possible approaches and presented them to provide context to the reader. The selected approaches were then justified based on our research objectives, the existing gaps in evidence, and the current decision-making frameworks in Australia. This study used a screening case study, although genetic and genomic tests are predominantly used in diagnostic settings. As the decision-making context and outcomes may differ substantially between screening and diagnostic applications, our findings may have limited generalisability. Further research is needed to evaluate the appropriateness of including intermediate outcomes in economic models in diagnostic settings.

### *Conclusions*

This study highlights the considerable impact of intermediate outcomes on cost-effectiveness results of NIPT, advocating for their consideration in genomics more broadly. This is the first study that we know of to incorporate monetary values of intermediate outcomes into a CUA and to compare the results to a NMBA. The results and potential policy implications were consistent across both analyses, with the CUA being a more practical approach given existing Australian HTA frameworks. Further research is needed to overcome the remaining theoretical economic concerns surrounding the use of WTP estimates for valuing intermediate outcomes, including these estimates in the cost side of a CUA and the acceptability of this approach to decision-makers. We propose that these methods could be used within scenario analyses and function as valuable tools to support decision-making about healthcare funding.

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## Supplementary materials

### Section A. Narrative review methods

*Embase search terms*

**Table 45. Embase search terms, search conducted on the 18th of July 2024**

| No. | Query |
|---|---|
| 1 | ("stated preference" or "conjoint analysis" or "DCE" or “discrete choice*” or "preference*" or "BWS" or "best-worst*" or "willingness to pay" or "WTP" or "discrete choice$" or "part-worth" or "part worth" or "paired comparisons" or "pairwise choice$" or "standard gamble" or "SG" or "time trade off" or "TTO").m_titl. |
| 2 | ("economic evaluation" or "economic modelling" or "health technology assessment" or "HTA" or "decision tree" or "Markov model" or "policy" or "cost-effectiveness" or "cost-benefit" or "cost-utility" or "cost-conseqence" or "decision making").m_titl. |
| 3 | #1 AND #2 |
| 4 | limit 3 to yr="2010" |

## Section B. Narrative review included studies

**Table 46. Narrative review included studies: how to incorporate stated preference research into decision-making?**

| Study ID | Title |
|---|---|
| Bouvy (2020)[1] | Use of patient preference studies in HTA decision making: A NICE perspective |
| Bridges (2023)[2] | A roadmap for increasing the usefulness and impact of patient-preference studies in decision-making: A good pracices report of an ISPOR taskforce. |
| Chachoua (2020)[3] | Use of patient preference information in benefit-risk assessment, health technology assessment, and pricing and reimbursement decisions: A systematic literature review of attempts and initiatives |
| Costa (2023)[4] | Patient preferences and cost-benefit of hypertension and hyperlipidemia collaborative management model between pharmacies and primary care in Portugal: A discrete choice experiment alongside a trial (USFarmacia) |
| Ghijben (2018)[5] | Patient-centered decision making: Lessons from multi-criteria decision analysis for quantifying patient preferences |
| Ghosh (2023)[6] | Moving towards people-centred healthcare systems: Using discrete choice experiments to improve leadership decision making |
| Govathson (2023)[7] | A modelling framework for translating discrete choice experiment results into cost-effectiveness estimates: An application to designing tailored and scalable HIV and contraceptive services for adolescents in Gauteng, South Africa |
| Hiligsmann (2024)[8] | HTA community perspectives on the use of patient preference information: Lessons learned from a survey with members of HTA bodies |
| Huls (2018)[9] | Patient preferences in health technology assessment: A systematic review and research agenda |
| Huls (2019)[10] | What is next for patient preferences in health technology assessment? A systematic review of the challenges |
| Jackson (2019)[11] | The evolving role of patient preference studies in health-care decision-making, from clinical drug development to clinical care management. |
| Kim (2023)[12] | Accounting for nonhealth and future costs in cost-effectiveness analysis: Distributional impacts of a US cancer prevention strategy |
| Kim (2024)[13] | MSR90 Incorporating patient preferences into mathematical and statistical models in health economics: A taxonomy of approaches |
| Lakdawalla (2017)[14] | Defining elements of value in health care—a health economics approach: An ISPOR Special Task Force Report |
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| Morrison (2023)[20] | HTA274 Similarities and differences in health technology assessment (HTA) bodies considerations for decision-making: Use of patient preference studies |
| Moro (2022)[21] | Evaluating discrete choice experiment willingness to pay [DCE-WTP] analysis and relative social willingness to pay [RS-WTP] analysis in a health technology assessment of a treatment for an ultra-rare childhood disease [CLN2]. |
| Mott (2018)[22] | Incorporating quantitative patient preference data into healthcare decision making processes: Is HTA falling behind? |
| Parke (2023)[23] | HTA132 Reporting patient preference studies in health technology assessment submissions: Does it make a difference? |
| PREFER consortium (2022)[24] | PREFER recommendations - why, when and how to assess and use patient preferences in medical product decision-making |
| Rodriguez-Leboeuf (2022)[25] | HTA270 Use of patient preference studies to support HTA submissions in oncology |
| Strauss (2022)[26] | The use ff discrete choice experiments for measuring patient preferences in health technology assessment |
| Stoniute (2018)[27] | Challenges in valuing temporary health states for economic evaluation: A review of empirical applications of the chained time trade-off method. |
| Thokala (2020)[28] | PMS13 Incorporating patient preferences in health technology assessment - is individual simulation modelling useful? |
| Tinelli (2015)[29] | What, who and when? Incorporating a discrete choice experiment into an economic evaluation |
| Whichello (2020)[30] | An overview of critical decision-points in the medical product lifecycle: Where to include patient preference information in the decision-making process? |

## Section C. Economic modelling results

*Model M5 full results*

**Table 47. Results from model M5 (microsimulation, 5 health states), including net marginal benefit and cost-utility analyses**

| Outcomes included | Test | Cost AUD 2024 | Incremental cost AUD 2023 | Effect | Incremental effect | Incremental results (ICER or NMB) | Outcome |
|---|---|---|---|---|---|---|---|
| **Cost-utility analysis** | | | | | | | |
| *Without intermediate outcomes* | cFTS | 282.13 | | 0.991639 | | ICER: -22,720 | NIPT is dominated (more expensive and less effective) |
| | NIPT | 283.70 | 1.57 | 0.991570 | -0.000069 | | |
| *With intermediate outcomes* | cFTS | 345.45 | | 0.991639 | | ICER: -40,244 | NIPT is dominated (more expensive and less effective) |
| | NIPT | 348.23 | 2.780886 | 0.991570 | -0.000069 | | |
| **Net marginal benefit analysis (1 QALY = 28,000)** | | | | | | | |
| *Without intermediate outcomes* | cFTS | 282.13 | | 27764.75 | | NMB: -3.12 | NIPT is not optimal |
| | NIPT | 283.70 | 1.57 | 27763.2 | -1.55372 | | |
| *With intermediate outcomes* | cFTS | 282.13 | | 27702.33 | | NMB: -4.94 | NIPT is not optimal |
| | NIPT | 283.70 | 1.57 | 27698.96 | -3.37372 | | |
| **Net marginal benefit analysis (1 QALY = 50,000)** | | | | | | | |
| *Without intermediate outcomes* | cFTS | 282.13 | | 49579.91 | | -4.34 | NIPT is not optimal |
| | NIPT | 283.70 | 1.57 | 49577.14 | -2.7745 | | |
| *With intermediate outcomes* | cFTS | 282.13 | | 49517.49 | | -6.16 | NIPT is not optimal |
| | NIPT | 283.70 | 1.57 | 49512.9 | -4.5945 | | |
| **Net marginal benefit analysis (1 QALY = $65,000)** | | | | | | | |
| | cFTS | 282.13 | | 64453.89 | | -5.18 | NIPT is not optimal |

| Outcomes included | Test | Cost AUD 2024 | Incremental cost AUD 2023 | Effect | Incremental effect | Incremental results (ICER or NMB) | Outcome |
|---|---|---|---|---|---|---|---|
| *Without intermediate outcomes* | NIPT | 283.70 | 1.57 | 64450.28 | -3.60685 | | |
| *Without intermediate outcomes* | cFTS | 282.13 | | 64391.46 | | -7.00 | NIPT is not optimal |
| | NIPT | 283.70 | 1.57 | 64386.04 | -5.42685 | | |

Abbreviations: AUD, Australian Dollar; cFTS, combined first trimester screening; ICER, incremental cost-effectiveness ratio; NIPT, non-invasive prenatal testing; NMB, net monetary benefit; QALY, quality-adjusted life year.

*Model D3 full results*

**Table 48. Results from model D3 (decision tree, 3 health states), including** net marginal benefit **and cost-utility analyses**

| Outcomes included | Test | Cost AUD 2024 | Incremental cost AUD 2023 | Effect | Incremental effect | Incremental results (ICER or NMB) | Outcome |
|---|---|---|---|---|---|---|---|
| **Cost-utility analyses** | | | | | | | |
| *Without intermediate outcomes* | cFTS | 142.81 | | 0.9989434 | | ICER:48,927 | NIPT is more expensive and more effective |
| | NIPT | 143.95 | 1.14 | 0.9989667 | 0.00002330 | | |
| *With intermediate outcomes* | cFTS | 205.82 | | 0.9989434 | | ICER:130,043 | NIPT is more expensive and more effective |
| | NIPT | 208.85 | 3.03 | 0.9989667 | 0.00002330 | | |
| **Net marginal benefit analysis (1 QALY = $28,000)** | | | | | | | |
| *Without intermediate outcomes* | cFTS | 142.81 | | 27970.42 | | NMB: -0.488: | NIPT is not optimal |
| | NIPT | 143.95 | 1.14 | 27971.07 | 0.65240 | | |
| *With intermediate outcomes* | cFTS | 142.81 | | 27907.40 | | NMB: -2.36 | NIPT is not optimal |
| | NIPT | 143.95 | 1.14 | 27906.18 | -1.21849 | | |
| **Net marginal benefit analysis (1 QALY = $50,000)** | | | | | | | |
| *Without intermediate outcomes* | cFTS | 142.81 | | 49947.17 | | NMB: 0.0250 | NIPT is optimal |
| | NIPT | 143.95 | 1.14 | 49948.34 | 1.16500 | | |
| *With intermediate outcomes* | cFTS | 142.81 | | 49884.16 | | NMB: -1.85 | NIPT is not optimal |
| | NIPT | 143.95 | 1.14 | 49883.45 | -0.70503 | | |
| **Net marginal benefit analysis (1 QALY = $65,000)** | | | | | | | |
| *With intermediate outcomes* | cFTS | 142.81 | | 64931.32 | | NMB: 0.3745 | NIPT is optimal |
| | NIPT | 143.95 | 1.14 | 64932.84 | 1.51450 | | |
| | cFTS | 142.81 | | 64868.31 | | NMB: -1.49 | NIPT is not optimal |

| Outcomes included | Test | Cost AUD 2024 | Incremental cost AUD 2023 | Effect | Incremental effect | Incremental results (ICER or NMB) | Outcome |
|---|---|---|---|---|---|---|---|
| *Without intermediate outcomes* | NIPT | 143.95 | 5.79 | 64867.95 | -0.35494 | | |

Abbreviations: AUD, Australian Dollar; cFTS, combined first trimester screening; ICER, incremental cost-effectiveness ratio; NIPT, non-invasive prenatal testing; NMB, net monetary benefit; QALY, quality-adjusted life year.

*Sensitivity analysis (model M5)*

**Table 49. One-way sensitivity analysis**

| Input | Current value | Sensitivity analysis input | Reference for range | CUA ICER Result (AUD per QALY gained) | | NMBA NMB results (AUD) | |
|---|---|---|---|---|---|---|---|
| | | | | Without intermediate outcomes | With intermediate outcomes | Without intermediate outcomes | With intermediate outcomes |
| Uptake of NIPT | 100% | 76% & 100% | HQO 2019[31] | 37,063 & -22,720 | 37,589 & -40,244 | 0.464 | -3.735 |
| Uptake of diagnostic testing after cFTS | 80% | 40% & 100% | Lindquist 2019[32] | 1,123,474 & 44,839 | -1,173,921 & 28,176 | -12.94 | 0.25 |
| Uptake of diagnostic testing after high cFTS | 90% | 40% & 100% | Lindquist 2019[32] | -15,736 & -24,381 | -44,449 & -51,725 | -2.96 | -3.82 |
| Uptake of diagnostic testing after NIPT | 80% | 40% & 100% | Lindquist 2019[32] | 1,991 & -49,335 | -12,653 & -109,285 | 3.78 | -3.66 |

Abbreviations: AUD, Australian Dollar; cFTS, combined first trimester screening; CUA, cost-utility analysis; ICER, incremental cost-effectiveness ratio; NIPT, non-invasive prenatal testing; NMB, net monetary benefit; NMBA, net marginal benefit analysis; QALY, quality-adjusted life year.

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# Chapter 7:

# Discussion and conclusions

This chapter presents discussion of the findings of this research. It outlines the main contributions of the work, highlighting how the content of each chapter addresses key challenges in economic modelling for genetic and genomic testing. It summarises the practical implications of the research for three key stakeholder groups: healthcare professionals, policymakers, and health economic researchers. It also presents the strengths and limitations of the work, gives recommendations for future research, and ends with a conclusion section.

## Thesis overview

The research was designed to examine the impact of different approaches to economic modelling of genetic and genomic tests and the potential for these to lead to different public funding decisions for these tests. It explored the impact of different model structures with differing levels of complexity on model findings and the policy implications of these choices, and how the use of a broader range of outcomes (especially intermediate outcomes) from genetic and genomic testing can be incorporated within economic models.

## Main findings and contributions

**Table 50** describes the pre-existing state of knowledge in relation to the content of the five chapters of this thesis, and highlights the novel contributions of this work, which are described in more detail in the subsequent sections.

**Table 50. What does this thesis add to the literature?**

| Chapter | What is already known? | What does this study add? |
|---|---|---|
| **Chapter 2: Review**<br>*Comprehensive review of economic models of genetic and genomic testing* | • The evidence base up to 2017 demonstrated that developing economic models in NGS tests has several challenges including: (1) complex model structure; (2) the selection of outcomes and costs; (3) data availability.<br>• Several other reviews focusing on specific clinical areas, populations, and scales or technologies have identified consistent challenges. However, no review has provided a synthesis of primary studies across genetic and genomic contexts. | • This study provides an updated evidence base across all contexts of genetic and genomic testing and evaluates the progress made in addressing the previously identified challenges.<br>• It shows that an increasing number of studies are using more complicated model structures and attempting to include broader outcomes, though they remain limited and inconsistent in their approaches.<br>• It shows that despite efforts to date, there is an ongoing need to solve the issues of complex model structures and selection of outcomes. |
| **Chapter 3: Modelling**<br>*Impact of structural differences on the modelled cost-effectiveness of non-invasive prenatal testing* | • There are numerous published economic models of NIPT, with varying cost-effectiveness results.<br>• These differences are hypothesised to be due to differences in parameters and context.<br>• In the broader economic modelling literature, different model structures have been shown to cause differing results.<br>• Structural uncertainty is being increasingly recognised, but there is a lack of guidance on how to overcome it. | • In economic evaluations of second-line NIPT for the detection of T21, variations in model structure are associated with large differences in ICER results, likely to influence policy decisions. These findings contrast with previous hypotheses suggesting structural variations do not influence results in this context.<br>• To capture the complexities of NIPT, this study recommends using a microsimulation with at least 5 health states, rather than a simpler decision tree with 3 health states.<br>• This study recommends the development of a reference model (standardised model used within a specific decision-making context) for prenatal screening to address structural uncertainty and improve model consistency.<br>• This study makes a unique contribution to the broader literature by demonstrating the impact of incremental changes on model findings and likely funding decisions. |

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| **Chapter 4: Focus groups**<br>*Public perspectives around prenatal screening of chromosomal abnormalities: A focus group study comparing metropolitan and rural/regional areas in Australia.* | • Prenatal screening is associated with a broad range of impacts on potential parents, beyond the clinical diagnosis.<br>• Clinicians in Australia are concerned about equity issues around NIPT, specifically low income and rural families, as well as misunderstandings.<br>• No study in Australia has compared metropolitan and rural perspectives since the introduction of NIPT. | • This study highlights widespread misconceptions about the purpose of NIPT (i.e., screening, not diagnosis) and the conditions assessed.<br>• There were distinct differences in attitudes between people living in metropolitan versus rural and regional locations, particularly with respect to the different elements of access to screening (cost, wait times and distance).<br>• This study demonstrates alignment between clinicians' concerns and community concerns, emphasising the need to address inequities across geographical locations and ensure access to pre-test information in NIPT implementation. |
| **Chapter 5: Discrete choice experiment**<br>*Australian preferences for prenatal screening: A discrete choice experiment comparing metropolitan and rural/regional areas* | • International preference studies, and a Western Australia-specific preference study, have identified a public preference for expanding the scope of NIPT.<br>• Within Australia, there is lower uptake of NIPT in rural areas, and MSAC have noted an MBS item number targeted towards these areas as a potential approach, although further information is required. | • Within Australia, preferences for scope of testing depend on the level of accuracy and vary by geographical location.<br>• Rural and metropolitan communities value prenatal screening features similarly, suggesting that lower rural uptake stems from access issues rather than differences in preferences.<br>• This study is the first to quantify Australian-wide preferences for features of prenatal screening through WTP estimates, which can be used within economic evaluations. |

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| **Chapter 6: DCE & modelling**<br>*Integrating intermediate outcomes into economic models: A case study using prenatal screening* | • NIPT has a broad range of outcomes beyond clinical diagnosis, but these are rarely considered in economic evaluations. Evaluations that attempt to include them have typically used a CBA.<br>• While incorporating WTP estimates into the cost-side of a CUA has been suggested, it has not been explored.<br>• Stated preference research is currently considered in an informal manner within HTAs in Australia, with the extent of its consideration being unclear. | • The inclusion of intermediate outcomes can have substantial impact on cost-effectiveness of NIPT and likely policy decisions.<br>• This study demonstrates the feasibility of using WTP estimates to value intermediate outcomes in a cost-utility analysis. This approach may be more practical than a NMBA or CBA.<br>• This provides an option for a more formal consideration of stated preference research within HTA. |

Abbreviations**:** CBA, cost-benefit analysis; CUA, cost-utility analysis; DCE, discrete choice experiment; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; MBS, Medicare Benefits Schedule; MSAC, Medical Services Advisory Committee; NGS, next-generation sequencing; NIPT, non-invasive prenatal testing; NMBA, net marginal benefit analysis; T21, Trisomy 21; WTP, willingness to pay.

*Chapter 2: Comprehensive review of economic models of genetic and genomic testing*

This chapter presented a comprehensive review of economic models of genetic and genomic tests published in 231 articles covering a range of clinical purposes. Decision trees and Markov models were the most common techniques, with a growing trend towards microsimulations. Only a small proportion of studies justified the modelling approach taken, and an even smaller proportion included intermediate or process outcomes.

Researchers have conducted several reviews of economic models in the field of genetics and genomics, focusing on different clinical areas, populations, and scales or technologies of testing.[1-5] This study expanded on earlier reviews by including economic models across multiple contexts of genetic and genomic testing, and provided an updated assessment of progress in addressing previously identified challenges, including (1) the issue of complex model structures and (2) the selection of outcomes. The key contribution of the current study was documentation of growing model complexity over time, evidenced by the increase in individual-based models and efforts to include process and intermediate outcomes. However, such models and studies including broader outcomes were in the minority and the approaches taken were inconsistent, highlighting the ongoing need for solutions to these problems, which informed the objectives of the current research.

The review showed that NIPT was the area with the largest number of published economic models, with differing modelling techniques used and wide variance in cost-effectiveness results (ranging from cost saving to USD1,278,330 per Down syndrome diagnosis). Based on these findings, NIPT was selected as the case study to be explored in the research.

*Chapter 3: Impact of structural differences on the modelled cost-effectiveness of non-invasive prenatal testing*

The objective of the research in this chapter was to assess the impact of different model structures on the cost-effectiveness of NIPT for the detection of Down syndrome, addressing the first key challenge (complex model structures). This work involved three stages: (A) a systematic review to identify published model structures; (B) building alternative model structures and applying consistent

parameters; (C) comparing model findings and discussing potential policy implications. Based on the findings of the review, four demonstration models were developed in TreeAge™ and populated with consistent parameters: Model D3 (decision tree with 3 health states); Model D5 (decision tree with 5 health states); Model M3 (microsimulation with 3 health states); and Model M5 (microsimulation with 5 health states). Across the models, the ICERs ranged from NIPT being dominated (Model M5) to USD54,983 (2023)/QALY gained (Model M3).

Previous reviews of economic evaluations of NIPT have been conducted, with the most recent concluding that variations in findings across studies can be primarily attributed to parameter and contextual factors.[6] The current study makes several key contributions to the literature on the economic evaluation of NIPT for detecting Down syndrome. First, it provides a more comprehensive evidence base for health economists, incorporating 12 additional studies and extracting more details on model structure than the previous review.[6] Second, it is the first study to build and compare multiple models of NIPT, revealing that variations in model structure result in substantial differences in ICER results, even when using the same parameters and contextual framework. Third, this study recommends the use of more complex model structures for NIPT (i.e., a microsimulation with five health states over a simpler decision tree with three health states), to better capture the full impact and cost-effectiveness of NIPT. Lastly, this study recommends the development of a reference model (a standardised model used within a specific decision-making context)[7] for prenatal screening to reduce structural uncertainty and improve model consistency.

While it is well established from studies outside NIPT and genetic and genomic testing that different model structures can lead to different results,[8-11] these studies did not identify the specific aspects of model structures that drove differences in results. The current study makes a unique contribution to the broader literature by demonstrating that incremental changes in model structure can have a substantial impact on model findings, which in turn can affect funding decisions.

*Chapter 4: Public perspectives around prenatal screening of chromosomal abnormalities: A focus group study comparing metropolitan and rural/regional areas in Australia.*

The objective of this chapter was to explore the attitudes, values, and beliefs relating to prenatal screening in Australia, and how perspectives differ between people living in metropolitan and rural/regional locations. Three focus groups were held in New South Wales, conducted face-to-face and online via videoconference, in both metropolitan and rural/regional areas. The study found an overall desire to undertake NIPT in all geographical locations, but misconceptions about the screening tests available and conditions assessed. There were distinct differences in attitudes between people living in metropolitan versus rural/regional locations, particularly with respect to the different elements of access to screening (cost, wait times and distance).

Since the introduction of NIPT, Australian studies have examined clinicians' views on prenatal screening and the experiences of those who have undergone NIPT, focusing on metropolitan and high-income families. This study makes two key contributions to the literature. First, it expands the evidence base by capturing the perspectives of rural and regional communities, revealing how their views differ from those in metropolitan areas. Second, it demonstrates that clinicians' concerns about the public's misunderstandings of testing and equity issues are justified. These findings confirm the need to reduce inequities across geographical locations and improve access to pre-test information in NIPT implementation.

Whilst not directly related to economic modelling methods, the work presented in this chapter was a vital step in informing the development of the DCE in Chapter 5, thus addressing key challenge 2 (Selection of Outcomes). The following attributes of prenatal screening were identified as relevant to the Australian community and included within the DCE: (1) scope of testing; (2) false positive rate; (3) false negative rate; (4) inconclusive results; (5) revealing the sex of the biological fetus; (6) number of screening tests per pregnancy; (7) wait times; and (8) cost of screening.

*Chapter 5: Australian preferences for prenatal screening: A discrete choice experiment comparing metropolitan and rural/regional areas.*

The objective of this component of the research was to quantify Australian preferences for features of prenatal screening, focusing on potential variations between metropolitan and rural communities, addressing key challenge 2 (Selection of Outcomes). This was achieved through a DCE with 328 participants located across Australia, which included quotas for rural participants. The DCE revealed common preferences for a test with a lower false positive rate, lower false negative rate, and lower cost, with little concern for the number of screening tests per pregnancy or information on the sex of the fetus. Rural participants showed a preference for a test with broader scope (three common trisomies, sex chromosome conditions and other rare conditions compared to three common trisomies) and a lower inconclusive rate, whereas these factors did not significantly influence preferences in the metropolitan group. Although rural participants preferred a test with a broader scope, this was only true while false positive rates were low.

While there is extensive literature from overseas assessing preferences for prenatal screening,[12] research on Australian-specific preferences is scarce. Local context is particularly important given the potential variations in prenatal screening availability, access and preferences by geographical location. A recently published DCE found women in Western Australia supported expanding from the scope of testing from the three common trisomies to over 100 genetic conditions.[13] The current study extends these findings, showing that Australians' preferences for the scope of testing, based on more feasible NIPT applications, depend on the level of accuracy and vary by geographical location. Another key finding is the similarity in the value metropolitan and rural communities place on features of prenatal screening. This suggests that the lower uptake of NIPT in rural areas is driven by inequities in access rather than differences in preferences. Lastly, this is the first study to quantify Australia-wide preferences for prenatal screening through WTP estimates. The WTP estimates presented in this study offer a pathway to directly integrate the impacts of intermediate outcomes into economic models.

*Chapter 6: Integrating intermediate outcomes into economic models: A case study using prenatal screening.*

The final research chapter brought together all components of the thesis, addressing both key challenges for economic modelling in genetic and genomic testing (selection of outcomes and model structure). Its objective was to explore methods for incorporating the impact of intermediate outcomes into economic models and to understand the impact on model findings and policy decisions. Specifically, the work presented in this chapter involved integrating WTP estimates of intermediate outcomes (derived from the DCE in Chapter 5) into selected economic models of NIPT developed in Chapter 3. Two approaches were explored, using the WTP estimates in a NMBA and a CUA. Based on the findings of Chapter 3, a microsimulation with five health states was determined to be the most suitable model (Model M5) for extension within the base-case analysis. Structural uncertainty was explored through the use of a decision tree with three health states (Model D3). In Model M5, within both the NMBA and CUA, the inclusion of intermediate outcomes substantially reduced the cost-effectiveness of NIPT but would be expected to have minimal effect on policy decisions. In Model D3, within both the NMBA and CUA, including intermediate outcomes decreased the cost-effectiveness of NIPT and its likelihood of public funding.

A substantial body of qualitative research highlights the broad range of impacts prenatal screening can have on pregnant couples, including the anxiety and stress caused by intermediate outcomes, such as false and inconclusive results.[14] Previous economic work has attempted to value these intermediate impacts in utilities using a time trade-off study, and then incorporate the resulting utility weights into a CUA.[15] This approach had minimal impact on model findings, which the authors hypothesised was due to the time trade methodology used, in which trading-off intermediate outcomes with death may be inappropriate. The current research took an alternative approach, valuing intermediate outcomes using WTP estimates, involving a trade-off with costs. It makes a unique contribution to the literature by demonstrating that, when using WTP estimates, intermediate outcomes associated with NIPT can substantially affect cost-effectiveness results, with expected impacts on policy decisions.

Within the broader literature, as described in the narrative review in Chapter 6, the extent to which stated preference research (such as DCEs) is considered within HTAs is unclear, and there has been a call for research that incorporates stated preference research directly into economic models.[1, 16, 17] This is the first study to include intermediate outcomes as WTP estimates (derived from a DCE) within a CUA and compare the results to a NMBA. This study finds the CUA approach to be viable, although concerns about consistency with the theoretical underpinning of CUAs remain.[18] Due to the current HTA framework within Australia, which prioritises the use of CUA, the CUA approach may be more practical to implement than the NMBA approach. Additionally, the research presented in this chapter reinforces the findings (Chapter 3) demonstrating the considerable impact of structural uncertainty on model findings and likely policy decisions.

## Implications of the research

The research findings have implications for the implementation of NIPT, as well as for the work of health economists and policymakers in the field of genetics and genomics.

### *Implications for NIPT*

#### *Policymakers*

This research demonstrates the similar value that metropolitan and rural communities place on the accuracy of prenatal screening, as well as the increased value rural communities place on expanded scope of testing and shorter wait times for NIPT. Despite these preferences, most NIPT occurs in metropolitan areas of Australia.[19, 20] This research highlights the need for policies targeting improved NIPT access in rural and regional areas, such as the implementation of an MBS item number for NIPT based on geographical location.

An MBS item number could be implemented in several ways. The focus group findings revealed that many pregnant women in rural and regional areas do not have access to ultrasounds (an essential component of cFTS), and that the requirement to travel could stop them from participating in prenatal screening. This suggests the real benefits of NIPT may come from its use as an initial test (i.e., with an MBS item number for first-line NIPT). It should be noted, however, that ultrasounds are

still required to check for structural abnormalities. Regional/rural participants' desire for NIPT increased with perceived risk, suggesting that this item number could be further restricted to higher-risk individuals (e.g., those aged over 35), which would likely reduce the MBS budget impact.

*Health service delivery*

This thesis highlights the complexity of preferences regarding the scope of conditions, along with misunderstandings surrounding both this scope and the purpose of NIPT (i.e., as a screening rather than a diagnostic test) among the public. To improve understanding of the test and test results, changes could be made to (1) the test information and (2) how pre-test information is disseminated. First, understanding could be improved by ensuring the test information itself is improved, for example, by excluding conditions with very high false positive rates. Second, clear and consistent pre-test information should be widely accessible. The focus group findings suggest the public are not concerned about who delivers the pre-test information, with the options presented including general practitioners, practice nurses, midwives, obstetricians and genetic counsellors (specialists in this area, but in short supply).[21, 22] Therefore, investing in training alternative providers, such as practice nurses, to deliver pre-test information could reduce misconceptions surrounding prenatal screening. Genetic counsellors could then be prioritised to those receiving high-risk results. Digital technologies targeted toward rural areas could be explored, such as telehealth consultations, mobile applications and online decision aids. These technologies would facilitate virtual support from healthcare professionals, improving access to information in these communities.

*Health economic researchers*

This thesis provides health economists with an evidence base for economic evaluation of second-line NIPT in the detection of Down syndrome. It also provides a structurally validated microsimulation model, which can be further developed to assess the cost-effectiveness of second-line NIPT. This model could be used to support future economic evaluations of NIPT, aiding in policy decisions about prenatal screening strategies. This is likely to be relevant within the Australian context due to the increasing use of NIPT, despite the fact that a 2019 request for public funding of NIPT was not

supported.[23] Furthermore, genome-wide NIPT is an area of policy consideration and generating public interest as the technology advances.[13, 24]

### *Implications for genetics and genomics more broadly (health economic researchers and policymakers)*

The field of genetics and genomics is complex and rapidly evolving, presenting significant challenges for existing HTA systems. This research focused on NIPT for Down syndrome as a case study, but the insights gained should inform a broader range of genetic and genomic testing contexts. For example, the results herein are applicable to the suggested expansion of NIPT to screen for over 400 genetic conditions[13, 24, 25] and the inclusion of WGS in newborn screening programs.[26-28] These developments are the subject of debate due to their likely substantial budgetary and population-wide ethical, legal and social implications.[29, 30]

As described in the Introduction (Chapter 1), in Australia, HTAs currently follow a structured assessment framework consisting of: (1) Context; (2) Clinical evaluation; (3) Economic evaluation; (4) Budget impact; and (5) Other relevant considerations.[31, 32] Evidence on broader testing outcomes, including findings from DCEs and other preference studies, are typically categorised under "Other relevant considerations", leading to inconsistencies in how such evidence is presented and therefore considered by policymakers.[33] Given the nature of genetic and genomic testing, Boutelle et. al.[34] suggest unique methods are needed to ensure the consideration of intermediate and process outcomes within evaluations. Building on this, the findings of the current research recommend a more structured approach to considering intermediate (and possibly process) outcomes by valuing them through WTP estimates. These estimates can then be incorporated directly into economic models using a scenario analysis via a CUA, rather than a (typical) CBA. This would modify the current HTA framework in Australia by expanding "(3) Economic evaluation" to integrate aspects currently considered in "(5) Other relevant considerations". By quantifying and directly incorporating intermediate outcomes into economic models, their impact becomes more transparent, potentially improving the consistency of their consideration in decision-making. Furthermore, this research shows that incorporating

intermediate outcomes in genetic testing economic evaluations can have a substantial effect on cost-effectiveness, and hence policy decisions, highlighting the need for their consideration.

As Boutelle et al.[34] and Johnson et al.[3] noted, determining optimal model structure is not a challenge unique to genomic testing. However, meeting this challenge requires a deeper understanding of testing complexities and the appropriate application of existing methods to manage them. The current research advances our understanding of model structures for second-line NIPT with varying levels of complexity and demonstrates that even in a relatively simplified case of genetic testing (detecting only Down syndrome), structural differences can substantially influence model outcomes. This underscores the need for investment in more sophisticated models when evaluating genetic and genomic testing. It also highlights the necessity for HTA committees to give greater consideration to structural uncertainty and provide more formal guidance on this issue. For instance, in the context of prenatal screening, the use of reference models to offer guidance and enhance model consistency is recommended.

## Strengths and limitations

### *Strengths*

The strengths of this research include its comprehensive and mixed-methods approach to integrating intermediate outcomes into economic models. At each stage, context-specific primary evidence was generated – from qualitative focus groups exploring Australian perspectives around prenatal screening, to stated preference research deriving WTP estimates for intermediate outcomes, and finally to constructing and populating Australian-specific economic models. This research builds upon solutions suggested in the existing literature, identifies incorporating WTP estimates into economic models using a CUA as a valuable but unexplored technique, and advances our understanding of how this approach impacts model findings and policy decisions. It then makes a comparison with the typical NMBS approach and discusses the feasibility of both approaches. These findings have implications for both NIPT and the broader fields of health economics and health policy in genetics and genomics.

### *Limitations*

This study has six key limitations, which are described below.

First, simplifications were made within the models evaluating NIPT. These models focused on second-line NIPT, for the detection of Down syndrome, over the pregnancy duration. The following factors were not considered: (1) a large proportion of clinicians offer first-line NIPT,[19] (2) current screening recommendations include the three common trisomies, with optional screening for sex chromosome conditions and other rare conditions,[35] and (3) prenatal screening is associated with lifelong impacts. The models described in this thesis are intended to illustrate how different model structures can affect results. Therefore, while the simplifications may introduce bias, they were deemed acceptable to ensure a more manageable and focused analysis, providing valuable insights that can be expanded upon in future research.

Second, the preferences derived from the DCE may not be representative of those of the Australian general population. The focus groups that informed the DCE were conducted in the state of New South Wales, rather than across the whole of Australia. Both the focus groups and the DCE included people of childbearing age with an interest in pregnancy. The choice of population should be based on the purpose of the research question, and this choice has the potential to influence preference results.[36] This research was designed to influence policy and funding decisions. Australian HTA guidelines recommend using general population preferences in economic evaluations.[31] We included the general public with an interest in pregnancy, acknowledging this differs from these guidelines. While policymakers recognise the value of patient preferences, uncertainty remains about how to incorporate and weight them against general population preferences. [33] Different approaches are taken internationally; for instance, the Netherlands recommends using patient preferences, in contrast to the Australian recommendation for general population preferences.[31, 33, 37] Furthermore, in the context of genetics and genomics, it has been argued that due to the complexity of testing, a patient population may be more appropriate, improving both understanding and engagement. Consequently, to balance between the two populations, the current research selected participants from the general population with an interest in pregnancy. A general population sample would be expected to lead to lower WTP

estimates, because the preferences of individuals not interested in pregnancy are likely to be less pronounced. Therefore, in Chapter 6, when incorporating the WTP estimates derived from the DCE, a range of lower values in sensitivity analyses were explored. To further understand potential differences in preferences, "experience with prenatal screening" was used as both interactive and main effects within the mixed logit model in Chapter 5.

Third, participants in the DCE may not have fully grasped the complexities and implications of prenatal screening, resulting in inconsistent or inaccurate preference results. The focus group findings highlight the difficulty of adequately informing participants about the purpose of prenatal testing (i.e., it is for screening, not diagnosis), the range of conditions tested and associated consequences. The DCE partially addressed misunderstanding of the purpose of testing by distinguishing between diagnosis and screening within the information provided to participants before they completed the choice tasks and within the tasks, and by explicitly including the levels of accuracy within each task. However, it remains unclear whether participants considered the impact of receiving false results. A more serious issue is the ability of participants to comprehend the scope of conditions that can be tested and their consequences. Given that it is currently hard for general practitioners to convey this information to pregnant individuals during in-person consultations,[38] it is unlikely that participants fully understood it within the DCE, which presents a simplified description of the range of conditions. This limitation links to the previous one about the appropriate choice of population, which can influence the level of understanding. Therefore, preferences for the scope of conditions should be interpreted with caution, considering the potential limits in participant understanding.

Fourth**,** there are various ways to model preferences, leading to uncertainty. Firstly, whilst evidence suggests that research participants treat opt-out options differently to intervention options, the specific choice structure that participants use is unclear and context-specific, making it difficult to determine the appropriate modelling approach.[39] For our research, the use of a nested logit model was considered; however, the cognitive interviews did not indicate that our participants used a hierarchical choice structure. Consequently, this was deemed an inappropriate assumption. Instead, a mixed logit

model was chosen, with an alternative-specific constant for the opt-out option, included as a main effect. Secondly, WTP estimates can be calculated in both the preference and WTP spaces. In health economics, it is common practice to calculate WTP in the preference space, with few studies adopting the WTP space approach.[40] In other fields, the WTP space approach is considered to provide more realistic results, although the preference approach often better fits the data.[41-44] Pragmatically, WTP was calculated in the preference space and, to account for potential biases, different WTP values were explored in sensitivity analyses.

Fifth, the appropriateness of valuing intermediate outcomes using WTP estimates from a DCE, for use in economic evaluations, is unclear. A previous NIPT economic evaluation derived utility estimates from a time trade-off study, in which intermediate and process outcomes were traded off against death.[15] This resulted in minimal impacts on utility, which does not align with the qualitative literature. This method of valuing outcomes did not substantially impact model findings. In contrast, in the current research, participants traded off these outcomes against cost, providing WTP estimates that were found to influence model findings. It remains unclear whether the WTP estimates value these outcomes realistically, and this study may have overestimated the WTP, resulting in inaccurate assessments of cost-effectiveness.

Sixth, the CUA and NMBA approaches have methodological and conceptual limitations, as discussed in detail in Chapter 6. In summary, the monetisation of outcomes in the CUA diverges from standard health economics principles, potentially causing confusion and double counting, though these issues could be mitigated with transparency. The DCE values intermediate outcomes based on the community's WTP. In contrast, public funding decisions are determined by policymakers' valuation of a QALY (i.e., their assessment of whether the ICER [incremental cost/incremental QALY] is acceptable). The approach taken in this research thus combined “demand” (community) and “supply” (policymakers) -side valuation methods, which may be inappropriate. With the NMBA, valuing final outcomes in monetary terms was difficult, with no consensus on the monetary value of a QALY in Australia. This uncertainty was explored through the use of different QALY values within a

scenario analysis. Lastly, the misalignment between the value of a statistical life year and a QALY compromises cross-sector comparability.[45]

## Future research

Drawing on the findings of this research and the associated limitations, four recommendations for future research are proposed.

1) **Development of a reference model for NIPT.** Expand the model of NIPT described in this thesis to include a broader range of conditions. This is relevant because there is demand for the continuing expansion of testing beyond the three common trisomies. Additionally, the model should account for process outcomes, such as wait times, which were valued in this research but not incorporated into the model. Consideration could also be given to extending the time horizon.
2) **Explore the development of separate models for metropolitan and regional/rural communities**. Develop separate models that consider different treatment pathways, such as including the option of first-line NIPT for rural communities and having ultrasound as a second test. These models should account for different uptake rates and WTP values for intermediate outcomes. This could help inform an MBS item number targeted to rural and regional communities.
3) **Explore the reliability of using WTP estimates of the community to value intermediate outcomes associated with prenatal screening.** The following questions should be examined:
    a) How do policymakers in Australia value prenatal screening intermediate outcomes? Do the WTP estimates of intermediate outcomes derived from this research, from the Australian community, align with those from Australian policy makers?
    b) How do WTP estimates differ between the Australian general population and patient population? (This research should explore the understanding of both populations.)
    c) Can this valuation method be applied internationally, specifically in countries such as the UK where health services are predominantly publicly funded?

4) **Assess the feasibility and acceptability of incorporating WTP estimates within a CUA framework for policymakers in Australia.** This research should evaluate the acceptability and potential challenges of using WTP estimates in a CUA from a policymaker's perspective. This research could be expanded to explore the views of policymakers in other countries.

## Conclusion

This research aimed to understand the impact of different approaches to economic modelling of genetic and genomic testing, focusing on two key challenges: (1) Model Structure and (2) Selection of Outcomes. Several key findings were obtained using (NIPT) as a case study, as outlined below.

The evaluation of different model structures with varying levels of complexity revealed substantial implications for model findings and subsequent policy decisions. Simpler models, whilst easier to build and interpret, failed to capture the full impacts of NIPT. In contrast, more complex models provided a more accurate representation of the full impacts but required greater resources and expertise. The choice of model structure plays a crucial role in shaping policy recommendations, suggesting that within the context of genetic and genomic testing, more complicated models are worth the additional investment.

Traditional models focusing on final health outcomes often overlook the impacts of intermediate steps in the genetic/genomic testing pathway. These broader outcomes can be incorporated directly into economic models through WTP estimates, within either a CUA or NMBA, which can affect cost-effectiveness results and have the potential to influence policy decisions. These findings support the formal consideration of intermediate outcomes within public funding decisions about genetic and genomic testing, providing a more comprehensive assessment of value.

In conclusion, this thesis offers new knowledge about two key challenges associated with health economic modelling in genetic and genomic testing, constituting valuable insights for health economic researchers and decision-makers.

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# Appendix – Publications during candidature

I contributed to five published studies outside of the thesis, either as first author or co-author, during my candidature:

- **Salisbury A**, Ciardi J, Norman R, Smit A, Cust A, Low C, Canfell K, Gordan L, Steinberg, J, & Pearce A. Public preferences for genetic and genomic risk-informed chronic disease screening and early detection: A systematic review of discrete choice experiments. *Applied Health Economics and Health Policy*. 2024; 1–14.
- Howard K, Norris S, **Salisbury A**, Pearce A, Ha, L, Stapleton B, Lean C, Last A, Kwedza R, White K, & Rushton S. Women's preferences for hypofractionated radiation therapy for treatment of early-stage breast cancer: A discrete choice experiment. *International Journal of Radiation Oncology* Biology* Physics*. 2024; 119(1): 172–184.
- Peasgood T, Howell M, Raghunandan R, **Salisbury A**, Sellars M, Chen G, Coast J, Craig J. C, Devlin N J, Howard K, & Lancsar E. Systematic review of the relative social value of child and adult health. *PharmacoEconomics*. 2024; 42: 177–198.
- Bailey C, Howell M, Raghunandan R, Dalziel K, Howard K, Mulhern B, Petrou S, Rowen D., **Salisbury S**, Viney R, & Lancsar E. The RETRIEVE checklist for studies reporting the elicitation of stated preferences for child health-related quality of life. *PharmacoEconomics*. 2024: 1–12. https://doi.org/10.1007/s40273-023-01327-x
- Bailey C, Howell M, Raghunandan R, **Salisbury A**, Chen G, Coast J, Craig J, Devlin N, Huynh E, Lancsar E, Mulhern B, Norman R, Petrou S, Ratcliffe J, Street D, Howard K, & Viney R. Preference elicitation techniques used in valuing children's health related quality of life: A systematic review. *PharmacoEconomics*, 2022; 40(7): 663–698.