UNIVERSITY OF TECHNOLOGY SYDNEY

Core Outcome Development for Carrier Screening (CODECS) Study: Towards a Core Outcome Set for Reproductive Genetic Carrier Screening

by Ebony Richardson

Thesis submitted in fulfilment of the requirements for the degree of

Doctor of Philosophy 95601 Genetic Counselling

under the supervision of:

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Declaration of original authorship

I, Ebony Richardson, declare that this thesis is submitted in fulfillment of the requirements for the award of the Doctor of Philosophy 95601 Genetic Counselling, in the Graduate School of Health at the University of Technology Sydney.

This thesis is wholly my own work unless otherwise referenced or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

This document has not been submitted for qualifications at any other academic institution.

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Abstract

Background: Reproductive genetic carrier screening (RGCS) provides prospective parents with information needed to understand their chance of having a child with a recessive genetic condition and informs reproductive decision-making. RGCS is well established in increased risk groups and is now transitioning to a population-based screening model with practice recommendations supporting its offer to all individuals planning a pregnancy or in the first trimester. Despite significant benefits being demonstrated in increased risk groups, there is little evidence regarding its impact when offered at population scale. Identifying and understanding which outcomes can meaningfully capture benefits and potential harms is key to informing the implementation of population-based RGCS. The Core Outcome Development for Carrier Screening (CODECS) study aims to establish a core outcome set (COS) for population-based RGCS. The COS is developed for use in any study offering RGCS at the population level, across various relevant study designs including observational studies and randomised controlled trials.

Methods: The steps of the CODECS study reported in this thesis are (1) a systematic review of quantitative studies evaluating RGCS, (2) a sequential systematic review of qualitative studies, (3) qualitative interviews with patient stakeholders, and (4) a Delphi survey of Australian and New Zealand stakeholders. These steps are per the framework established by the COMET initiative.

Results: The systematic review of quantitative studies identified 120 outcomes assessed in studies of RGCS (n=48). Outcome heterogeneity, bias and lack of patient-reported outcome measures were evident, and these provide a strong rationale for the development of a COS. The systematic review of qualitative studies (n=13) and qualitative interviews with patient stakeholders (n=15) identified outcomes of importance to patients that were not reflected in the quantitative literature, which indicates that further work is needed to ensure outcomes relevant to patients are incorporated into research. Collated outcomes were reviewed in a Delphi survey of 12 expert panellists. Eight outcomes reached consensus regarding their critical

importance for inclusion in all future studies and were used to define a preliminary COS: (1) carrier and couple detection rates, (2) uptake of prenatal diagnosis, (3) decision to continue or terminate affected pregnancies, (4) uptake of partner testing, (5) uptake of post-test genetic counselling, (6) reproductive decisions made by patients post-test and long term, (7) reproductive empowerment, and (8) affected individuals born to patients that accessed RGCS.

Conclusion: The development of a COS facilitates a structured and rigorous approach to identifying 'what to measure'. This research identified significant gaps in the evidence base for population-based RGCS and highlighted the importance of assessing outcomes relevant to these gaps to inform implementation. The need for a patient-centred approach to outcome selection was central to the findings, with the incorporation of outcomes of importance to patients having the potential to enhance translation of research findings into clinical practice. A COS can address existing issues with research waste and ensure that future studies work towards a common goal of evidence-based practice recommendations. The findings presented here are crucial to inform the implementation of population-based RGCS and ensure best care for patients.

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Statement of format of thesis

This thesis is presented as a thesis by compilation. It comprises an introduction in Chapter 1, presents the study design and methodology in Chapter 2, describes four separate studies in Chapters 3–6, and presents the discussion and conclusions in Chapter 7. I wrote all of the text in the thesis and revised it after feedback from my supervisors, Dr Chris Jacobs, A/Prof Alison McEwen and Prof Toby Newton-John. Chapters 2–5 provide, with permission, the accepted manuscripts of four peer-reviewed articles. Chapter 6 includes one manuscript currently under consideration and may not represent the final published form of this work. The referencing format for the manuscripts has been adapted where appropriate for consistency across the thesis and, where appropriate, spelling has been changed from US English to Australian English. The numbering and labelling of the tables, figures and supplementary files has been updated to be consistent across the thesis. Supporting information for each chapter is provided in the appendices.

List of publications arising from this research

Richardson E, McEwen A, Newton-John T, Manera K, Jacobs C. The Core Outcome DEvelopment for Carrier Screening (CODECS) study: protocol for development of a core outcome set. Trials. 2021;22(1):480. doi: https://doi.org/10.1186/s13063-021-05439-7

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Richardson E, McEwen A, Newton-John T, Crook A, Jacobs C. Incorporating patient perspectives in the development of a core outcome set for reproductive genetic carrier screening: a sequential systematic review. Eur J Hum Genet. Mar 28 2022;30:756-765. doi: https://doi.org/10.1038/s41431-022-01090-1

Richardson E, McEwen A, Newton-John T, Crook A, Jacobs C. Outcomes of importance to patients in reproductive genetic carrier screening: A qualitative study to inform a core outcome set. J Pers Med. 2022;12(8):1310. doi: https://doi.org/10.3390/jpm12081310

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Statement of contribution of authors

- Contribution of graduate research student Ebony Richardson: lead author
- Contribution of Dr Chris Jacobs: primary supervisor, joint author
- Contribution of A/Prof Alison McEwen: co-supervisor, joint author
- Contribution of Prof Toby Newton-John: co-supervisor, joint author
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Richardson E (2021) Is research wasteful? Making a case for core outcome sets. Paper presented at: UTS Faculty of Health 3 Minute Thesis Competition; June 15th, 2021; Sydney, Australia.

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Richardson E., McEwen A., Newton-John T., Manera K., Crook A., Jacobs C. (2021) Developing a core outcome set for reproductive genetic carrier screening: A new approach to understanding outcomes in genetics. Paper presented at: The World Congress on Genetic Counselling; 27th October, 2021; Virtual conference.

Richardson E., McEwen A., Newton-John T., Crook A., White S., Jacobs C. (2022) The Core Outcome DEvelopment for Carrier Screening (CODECS) Study: Results of an AUS/NZ Pilot Delphi Survey. Paper presented at: Human Society of Australasia (HGSA) annual scientific meeting; November 26th, 2021; Perth, Australia.
Awarded the Australasian Society of Genetic Counsellors (ASGC) prize for best poster presentation

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NSW Genetic Counsellor Quarterly Meeting 2019
Richardson E. (2019) Is there a role for core outcome sets in genetic counselling research? An overview of outcomes and thoughts regarding reproductive carrier screening.

Australasian Society of Genetic Counsellors Monthly Webinar Series 2022
Richardson E. (2022) Translating research findings into clinical practice: Potential benefits of a core outcome set.

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List of abbreviations

Abbreviation	Term
ACCE	Analytic Validity, Clinical Validity, Clinical Utility and Ethical, legal and social implications
ACMG	American College of Medical Genetics
ACOG	American College of Obstetricians and Gynaecologists
ASGC	Australasian Society of Genetic Counsellors
AUS	Australia
CGS	Clinical genetic services
CODECS study	Core Outcome Development for Carrier Screening study
COMET	Core Outcomes Measures in Effectiveness Trials
COREQ	Consolidated Criteria for Reporting Qualitative Research
COS	Core outcome set
COS-STAD	Core Outcome Set-Standards for Development
COS-STAP	Core Outcome Set-Standardised Protocol Items
COS-STAR	Core Outcome Set-Standards for Reporting
CVS	Chorionic villus sampling
FOCUS-GC	Framework for Outcomes of Clinical Communication Services in Genetic Counseling
GCOS-24	Genetic Counselling Outcomes Scale
GOS	Genomic Outcomes Scale
GP	General practitioner
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
GSH	Graduate School of Health
HGSA	Human Genetics Society of Australasia
HREC	Human Research Ethics Committee
HTA	Health technology assessment
IVF	In vitro fertilisation
MCH	Mean corpuscular haemoglobin
MCV	Mean corpuscular volume
MMIC	Multi-Dimensional Measure of Informed Choice
NHMRC	National Health and Medical Research Council

NIHR	National Institute for Health Research
NSGC	National Society of Genetic Counselors
NZ	New Zealand
OMERACT	Outcome Measures in Rheumatology
ORBIT	Outcome Reporting Bias in Trials
PACER	Patient-Centred Research Network
PCORI	Patient-Centered Outcomes Research Institute
PGD	Preimplantation genetic diagnosis
PICO	Patient/Population, Intervention, Comparison and Outcomes
PND	Prenatal diagnosis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
RANZCOG	Royal Australian and New Zealand College of Obstetricians and Gynaecologists
RCT	Randomised controlled trial
RGCS	Reproductive genetic carrier screening
SAG	Study Advisory Group
SMG	Study Management Group
SOGC-CCMG	Society Of Obstetricians and Gynaecologists of Canada Genetics Committee and the Canadian College of Medical Geneticists Clinical Practice Committee
SONG	Standardised Outcomes in Nephrology
SPOR	Strategy for Patient-Oriented Research
TOP	Termination of pregnancy
UAE	United Arab Emirates
UK	United Kingdom
USA	United States of America
UTS	University of Technology Sydney

Glossary of terms

Term	Definition
Consensus-based practice recommendations	Practice recommendations that have drawn evidence primarily from the opinions of key stakeholders; often due to a lack of available empirical evidence to inform the recommendation.
Couples	The term 'couple(s)' is used throughout this thesis to describe a broad range of family structures with a desire to have children. The phrasing 'couple' refers to the genetic parents of a current or future planned pregnancy
Evidence-based practice recommendations	Practice recommendations informed by a body of empirical evidence that can be trusted to guide practice
Genetic counselling*	The National Society of Genetic Counselors (NSGC) defines genetic counselling as "*Genetic counselling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates the following: (1) Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence. (2) Education about inheritance, testing, management, prevention, resources and research. (3) Counselling to promote informed choices and adaptation to the risk or condition*". Genetic counselling can be provided by genetic counsellors and other health professionals (e.g. clinical geneticists, neurologists).
Genetic counsellor	Allied health professionals with a tertiary qualification specialising in the practice of genetic counselling. The US spelling "genetic counselor" is used where appropriate, such as where professional organisations or journals use this spelling.
Genetic health intervention	The term genetic health intervention is used throughout this thesis to categorise health interventions that are specifically genetic in nature, including genetic counselling and genetic testing. The aims of such health interventions are defined below.
Health intervention□	"*A treatment, procedure, or other action taken to prevent or treat disease, or improve health in other ways*".

In vitro fertilisation with preimplantation genetic diagnosis (IVF/PGD)	IVF/PGD is an option available to couples wishing to prevent passing a known genetic condition onto their future children. Utilising IVF technology, embryos are tested prior to implantation to determine whether they have inherited the pathogenic variant(s) responsible for the genetic condition of concern, with only unaffected embryos being transferred. This technique ensures that the pathogenic variant(s) identified in a family cannot be passed on to future family members.
Outcome[§]	Health outcomes, referred to as 'outcomes' for brevity throughout this thesis, are "*the health consequences brought about by the treatment of a health condition or as a result of an interaction with the healthcare system. It is a multidimensional concept that can be studied on multiple levels*."
Outcome domain[**]	Outcome domains are defined as "*concepts to be measured in terms of a further specification of an aspect of health*". These are less granular or overarching categories that can be used to group similar or related outcomes. For example, the domain of psychological wellbeing can be used to capture a range of specific outcomes such as anxiety, depression, and grief.
Patient	A patient is any recipient of health care services that are performed by healthcare professionals.
Patient participants	Patients who contributed to research by participating in specific aspects of a study.
Patient research partner	Patients who contributed to research as active partners in the design, conduct and analysis of a study.
Population-based RGCS	The universal offer of RGCS to the general population.
Preconception	The time period before conception of a pregnancy. In the context of RGCS, preconception offers provide the greatest number of reproductive options to couples if identified as increased risk.
Prenatal	The time period commencing from the conception of a pregnancy. In the context of RGCS, prenatal offers limit the reproductive options available in the current pregnancy at the time of testing and present additional challenges regarding timing, deliberation and informed decision-making.

Prenatal diagnosis (PND)	An invasive genetic test performed during early pregnancy to obtain a genetic sample from a fetus for genetic testing. A sample of the placenta (chorionic villus sampling) or amniotic fluid (amniocentesis) is taken transabdominally or transvaginally and tested for specific genetic conditions of concern and broadly screened for chromosomal abnormalities using a microarray. This reproductive genetic testing technique is available to increased risk couples following RGCS who wish to conceive a pregnancy naturally and test to determine the affectation status, with the option to continue or terminate an affected pregnancy in line with their personal values.
Prospective parents	This term refers to the intended parents of a future child and considers a broad range of family structures. Prospective parents may be the genetic parents of a current or future planned pregnancy or may refer to same-sex couples or other family structures where both prospective parents are not contributing genetic material to the pregnancy. The breadth of this term is intended to recognise the diverse ways in which families may be created, including the use of surrogates and donor gametes.
Reproductive genetic carrier screening (RGCS)	RGCS is a screening test carried out before pregnancy or in early pregnancy to identify a couple's chance of having a child with a serious genetic condition.
Targeted RGCS	The targeted offer of RGCS to specific groups with an increased incidence of specific genetic conditions

* Definition taken from Resta R, Biesecker B, Bennett R, et al. A new definition of genetic counseling: National society of genetic counselors' task force report. J Genet Counsel. 2006;15(2):77-83. doi: https://doi.org/10.1007/s10897-005-9014-3

□ Definition taken from the National Institute of Health (NIH)

§ Definition taken from Lee, A., Leung, S. (2014). *Health Outcomes*. In: Michalos, A.C. (eds) Encyclopedia of quality of life and well-being research. Springer, Dordrecht. doi: https://doi.org/10.1007/978-94-007-0753-5_1251

** Definition taken from Boers M, Kirwan JR, Wells G, et al. Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. *J Clin Epidemiol*. 2014;67(7):745-753. doi: https://doi.org/10.1016/j.jclinepi.2013.11.013

Chapter 1: Introduction

1.1 Thesis overview

This thesis is presented as a series of chapters outlining four sequential studies that address an overall aim to develop a core outcome set (COS) for reproductive genetic carrier screening (RGCS). This work is together referred to as the Core Outcome Development for Carrier Screening (CODECS) study. Herein I will report on the steps of the CODECS study that were completed within the scope of this thesis.

1.2 Chapter overview

This chapter will introduce the genetic counselling profession and its relevance to this thesis, present some background of RGCS, explore the current practice recommendations and guidelines, and introduce the concept of a COS. It contains the background section of a published protocol, interspersed with additional content, please refer to the below reference to see the peer-reviewed version in full. The remainder of the protocol is presented in Chapter 2: Research Methods:

> Richardson E, McEwen A, Newton-John T, Manera K, Jacobs C. The Core Outcome DEvelopment for Carrier Screening (CODECS) study: protocol for development of a core outcome set. *Trials*. Jul 22 2021;22(1):480. doi: https://doi.org/10.1186/s13063-021-05439-7

1.3 Genetic counselling

This section summarises the relevance of my profession as a genetic counsellor to this thesis.

1.3.1 Genetic counselling as a profession

As defined by the National Society of Genetic Counselors (NSGC), "Genetic counselling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates the following: (1) Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence. (2) Education about inheritance, testing, management, prevention, resources and research. (3) Counselling to promote informed choices and adaptation to the risk or condition".[1] There is a distinction to be made between the definition of genetic counselling as a process and the role of genetic counsellors.

Whereas the process of genetic counselling relates explicitly to its application in clinical settings, the roles that genetic counsellors can contribute to outside the clinical setting are expanding. Many genetic counsellors now work in research, laboratory, industry, educational, policy and advocacy roles.[1-8]

Many clinical genetic counsellors conduct and participate in research as one element of their role. The recognition of the valuable contribution made by genetic counsellors to the research process has led to increasing numbers of genetic counsellors taking up full-time research roles and participating in post-doctoral studies to further their research expertise.[3,4] The training and skills implicit to genetic counsellors bring a new perspective to the research field, which may shift the research agenda, bring a patient-centred approach and overcome barriers to translating research findings into practice.[9]

Much genetic counselling research focuses on evaluating aspects of the genetic counselling process. More recently, given the calls from overarching healthcare organisations for demonstration of the benefits of health interventions to inform funding and resource allocation, there has been an increasing need to demonstrate the value of genetic counselling, clinical genetic services and genetic testing.[10-12] For brevity, I subsequently refer to genetic counselling, clinical genetic service use and genetic testing broadly under the term of genetic health interventions. Demonstrating value requires clear definitions of the outcomes that can capture benefits and potential harms of genetic health interventions.[13,14] Several systematic reviews have aimed to identify relevant outcomes and their measurement methods.[12,15,16] A lack of consensus about which outcomes can meaningfully capture benefit, variable measurement methods and issues with methodological rigor have been identified and informed subsequent research efforts to improve the rigor of future research.[17,18] Of note, existing research into the outcomes of genetic health interventions has been strongly genetic counsellor led.[10,18]

As a genetic counsellor, my interest in defining the outcomes of genetic health interventions stems from the same underlying desire that has informed previous research; that is, to provide a clear pathway for demonstrating the value of our profession and the genetic health interventions that we facilitate for our patients. The patient-centred perspective inherent to the genetic counselling profession recognises both the clinical outcomes that are important from a medical perspective and the more difficult-to-conceptualise personal outcomes that impact our patients. Such personal outcomes are crucial elements of the value that genetic health interventions provide. This thesis builds

on existing efforts to understand the most appropriate outcomes of genetic health interventions that will allow genetic counsellors to thrive within a value-based healthcare and funding system.

1.3.2 Relevance of my profession to this thesis

It is important to position myself in this thesis and outline my relevant experience and background. I am an associate genetic counsellor with 7-years' experience working in genetic counselling roles across clinical, research and laboratory settings. In 2015, I took a clinical role based in a private ultrasound service offering preconception and prenatal genetic counselling. In this role, I saw individuals and couples who were striving towards the goal of a healthy pregnancy. I provided access to testing to understand the chance of a genetic condition occurring in a future or current pregnancy and facilitated adaptation of the information provided by such tests. These tests included genetic tests such as RGCS, non-invasive prenatal screening (NIPS) and prenatal diagnosis via chorionic villus sampling (CVS) or amniocentesis, as well as interpretation of non-genetic tests including first-trimester nuchal screening and second-trimester morphology ultrasounds to inform genetic testing decision-making.

In this role, I first developed an interest in RGCS, which was newly available in Australia via commercial offerings at the time. I was involved in the implementation of RGCS in clinical practice and was interested in the impact of this new intervention on my patients and their reproductive decision-making. I also saw the inequity of access because of the cost of RGCS, which contrasted starkly with the valuable information provided by this testing. As such I was both an advocate for RGCS while recognising the need for improvements in accessibility and implementation that could maximise its benefit for patients. I also had the opportunity to participate in research as part of this role and gained an appreciation of the importance of evaluating the health interventions offered in practice. Despite leaving this role in 2018, I maintained a keen interest in RGCS and continued to follow updates about its availability in Australia and internationally.

In 2018, the Australian government announced a $20 million study title 'Mackenzie's Mission' to determine the evidence for making RGCS freely available through a publicly funded program to all couples in Australia who wish to have it.[19] This marked an important milestone in the transition of RGCS to a population-based screening option that could recognise the vast potential of RGCS in an equitable and accessible way. Therefore, when the opportunity to undertake a PhD arose, I knew that my previous experience in RGCS and the changing landscape of RGCS would inform my research direction.

1.4 Reproductive genetic carrier screening

This section will provide an overview of RGCS and the rationale for choosing this as a specific area for exploring the appropriate outcomes to capture value of genetic health interventions.

1.4.1 Purpose of RGCS

RGCS is one of the most widely adopted genetic tests worldwide and provides individuals and couples with information about their risk of having a child with a genetic condition before or during early pregnancy.[20] RGCS identifies carriers of recessively inherited conditions (autosomal recessive or X-linked), such as cystic fibrosis, spinal muscular atrophy and Fragile X syndrome. These conditions often arise unexpectedly, and carriers are, in most instances, asymptomatic. Because the reproductive risk usually increases only if a carrier partners with a carrier of the same condition, most couples that have an affected child do not have an existing family history that could have forewarned of their risk.

Recessively inherited conditions are individually rare but, when combined, are estimated to affect at least 30 in every 10,000 or 0.3% of live births.[21,22] Based on this birth prevalence, it is estimated that 1-2% of couples will be at risk of having a child affected by a genetic condition, and this number can be much higher in consanguineous populations.[23] Of those at increased risk, the likelihood of having an affected child is 25%-50% in each pregnancy, depending on the specific condition. The intent of RGCS is to provide couples who are at increased risk with the information needed to allow them to make informed reproductive decisions. Those who are aware of their risk can choose to pursue prenatal diagnosis during pregnancy, opt for in vitro fertilisation (IVF) with preimplantation genetic diagnosis or the use of a donor gamete, consider adoption or pursue pregnancy without any intervention and diagnose postnatally if desired.

For this thesis, individuals and couples undertaking RGCS are referred to as patients to reflect the clinically significant nature of the information provided through RGCS. However, I acknowledge that these are mainly healthy adults, most of whom will not go on to require significant medical follow-up based on their carrier screening results.

1.4.2 History of RGCS

Carrier screening programs have been implemented since the 1970s in populations that have increased carrier frequencies for certain conditions, and targeted testing has been

used only for the conditions relevant to that population. Such conditions include, but are not limited to, Tay-Sachs disease in the Ashkenazi Jewish population and thalassaemia and other inherited haemoglobinopathies across a range of ethnicities.[24-26] These programs pre-dated the ability to identify carriers through genetic testing and instead relied on biochemical assays; cystic fibrosis was one of the first conditions to have a screening program based on molecular methods introduced in the 1990s.[27]

Early carrier screening programs typically focused on one genetic condition; however recent advances in genetic technologies have enabled a shift in the breadth of RGCS. Next-generation sequencing has facilitated the development of expanded panels that analyse hundreds to thousands of genetic conditions in a single laboratory test. These expanded panels are available to the general population predominantly through commercial offerings, which has limited uptake to high-income groups.

Individuals and couples may access RGCS in a range of ways, including community screening programs in populations at increased risk, attending public or private prenatal services during early pregnancy or accessing preconception care through general practitioners or genetic counsellors in the public or private sectors. Efforts to explore the feasibility of publicly funded RGCS offered universally to the general population are also underway and will inform the availability of more equitably accessible RGCS in the future.[19,28,29] With the building momentum of RGCS moving from a targeted screening offer to a widely available screening offer, it is a pivotal time to evaluate the value of population-based RGCS and consider where best to focus research efforts to inform implementation at population scale.

1.4.3 Definition and scope of RGCS

Although RGCS is a standalone test that is conducted at a specific point in time, for the purpose of this thesis, I considered RGCS to include the period leading up to accessing RGCS (information provision and pre-test genetic counselling), receiving and adapting to the results in the short term (post-test genetic counselling), and the long-term period of managing the implications of having accessed this health intervention (e.g. long-term goal of a healthy pregnancy in couples at increased risk). Pre- and post-test time periods, as well as long-term implications are important to capture to demonstrate the value of RGCS.

1.4.4 Current context of RGCS

Since the start of my PhD, the context of RGCS has evolved significantly in many ways. This information is relevant to the reader when reading the later chapters of this thesis.

Increasing public awareness and interest in RGCS

When I began my PhD, public awareness and interest in RGCS were limited. International studies had shown a discrepancy between positive attitudes or intentions to accept a RGCS and its actual uptake when offered.[30-32] The commercial nature of most offers, which necessitates significant out-of-pocket costs for patients, was a recognisable barrier to uptake. Specific to the Australian context and my own experience, the companies offering RGCS were based internationally and there was a lack of clarity about how to access these offers and long waiting times for results. In addition, there was a recognised lack of awareness among both patients and clinicians about why RGCS would be valuable outside of increased risk groups and a need for education about the potential benefits of a pan-ethnic screening approach.[33,34]

The announcement of Mackenzie's mission marked a significant shift in awareness of RGCS principally in Australia but also worldwide. Mackenzie's mission is the first example of an attempt to evaluate the acceptability and feasibility of government-funded RGCS program screening.[19] The story behind Mackenzie's mission is an emotive one and was widely publicised through media bodies. Mackenzie Casella, the daughter of Rachael and Jonathan Casella, was diagnosed with spinal muscular atrophy (SMA), an autosomal recessive genetic condition. Her parents were unknowingly carriers of this genetic condition and were not offered, nor made aware of, the opportunity for RGCS before or during their pregnancy. Sadly, Mackenzie died at just 7 months of age. This experience spurred the Casellas to become vocal advocates for RGCS, and they became a driving force behind lobbying of the Australian government that eventually led to the funding for Mackenzie's mission, also known as the Australian Reproductive Genetic Carrier Screening Project. Since 2018, the Mackenzie's mission team have successfully offered RGCS for a panel of over 1000 genes to 8,350 couples across Australia.

The significance of increasing the awareness of the availability of RGCS to the general population is that its uptake is likely to increase. Given the lack of evidence to demonstrate the impact of population-based RGCS, it is crucial to ensure that appropriate outcomes are assessed for informing implementation.

Recognition of key differences when offering population-based RGCS

Over the course of my PhD, discussions within the field of RGCS have shifted to considering the implications of population-based RGCS programs in comparison with existing targeted offers in increased risk groups. Key differences are now recognised and include understanding how the goals of population-based RGCS are conceptualised and how the societal context in which RGCS is offered can impact these goals. A bioethical critical analysis undertaken in parallel with Mackenzie's mission identified the importance of balancing the clinically focused goal of reproductive autonomy most often attributed to RGCS with the public health implications of a population-based offer.[35] Balancing values that can be drawn from both clinical and public health settings is complex but is necessary to support the reproductive autonomy of patients undertaking RGCS while maintaining an appreciation of the social factors that can impede their reproductive choices. A notable example is the overturning of Roe vs Wade in the USA which has the potential to significantly undermine the goal of reproductive autonomy.[36] This development, which criminalises the termination of pregnancy in many states across the USA, limits the reproductive options available to patients after accessing RGCS. For many, this eroding of choice undermines the goals of RGCS at their foundation. The societal context of a population-based screening offer is important to consider when identifying which outcomes are important to assess in this setting.

1.5 Practice guidelines and recommendations

This section addresses the current practice recommendations relevant to the offer of RGCS and explores their limitations.

1.5.1 Support for the offer of RGCS

There is increasing support for RGCS to be offered widely. In 2016, the Society of Obstetricians and Gynaecologists of Canada Genetics Committee and the Canadian College of Medical Geneticists Clinical Practice Committee (SOGC-CCMG) released a joint practice recommendation supporting the discussion of RGCS with all women/families considering pregnancy or at their first prenatal visit.[37] This advice was closely followed by a similar practice recommendation from the American College of Obstetricians and Gynaecologists (ACOG) in 2017.[38,39] These international organisations were amongst the first to support the widespread offer of RGCS outside of increased risk

populations, and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) followed suit in March 2019.[40]

1.5.2 Limitations of current recommendations

Practice recommendations are developed through multidisciplinary panels comprising all relevant stakeholders who conduct a rigorous and systematic review of the scientific evidence to determine the recommendation that will be provided for clinical practice.[41] These recommendations are usually graded to reflect the quality of evidence available to inform them and to allow critical evaluation by practitioners regarding whether to adopt the recommendation into their practice. Table 1 contains the grading reported for the three aforementioned practice recommendations from Canada, USA, and Australia and New Zealand.

The current practice recommendations on RGCS have several limitations. These are considered in Table 2 in relation to the National Health and Medical Research Council (NHMRC) standards for the development of guidelines, with a focus on Standard 5, which states that guidelines should "be focused on health and related outcomes" and Standard 6, which states that guidelines should "be evidence informed".[42] The NHMRC is an independent statutory agency that operates as part of the Australian government and is responsible for issuing practice recommendations, maintaining high standards of integrity and rigor in scientific research, and providing funding opportunities for Australian researchers.[43] Although direct equivalents do not exist, similar organisations responsible for practice recommendations and/or funding include the National Institute of Health (NIH)[44] and Centers for Disease Control and Prevention (CDC)[45] in the USA and the National Institute for Health and Care Research (NIHR)[46] and National Institute for Health and Care Excellence (NICE)[47] in the UK.

Table 1: Summary of evidence levels in recent practice recommendations

Practice Guideline	Country	Recommendation	Grading of Evidence	Interpretation of Evidence
SOGC-CCMG[37]	Canada	*"A primary discussion about the value and risk of reproductive carrier screening should be offered to all women/families considering a pregnancy (preconception) and to all pregnant women at their first prenatal visit, regardless of gestational age at the time of presentation."* p.744	Grading of Recommendations, Assessment, Development and Evaluations (GRADE) low/moderate	The GRADE level of low indicates that "the true effect may be markedly different from the estimated effect" and moderate that "the authors believe that the true effect is probably close to the estimated effect"[48]
ACOG[38]	USA	*"Ethnic-specific, pan-ethnic, and expanded carrier screening are acceptable strategies for pre-pregnancy and prenatal carrier screening. Each obstetrician-gynaecologist or other healthcare provider or practice should establish a standard approach that is consistently offered to and discussed with each patient, ideally before pregnancy. After counseling, a patient may decline any or all carrier screening."* p.595	No grading of the evidence used to inform this recommendation was provided	The lack of evidence grading suggests that the rigor with which existing evidence was reviewed may not be at the level expected of practice recommendations.
RANZCOG[40]	Australia and New Zealand	*"Information on carrier screening should be offered to all women planning a pregnancy or in the first trimester of pregnancy. Options for carrier screening include screening with a panel for a limited selection of the most frequent conditions (e.g. cystic fibrosis, spinal muscular atrophy and fragile X syndrome) or screening with an expanded panel that contains many disorders (up to hundreds)."* p.4	Consensus based	NHMRC Levels of Evidence and Grades of Recommendations for Developers of Guidelines[49] defined consensus-based recommendations as "Recommendation based on clinical opinion and expertise as insufficient evidence available"

Table 2: Evaluation of current practice recommendations against NHMRC standards for guideline development

Limitation	NHMRC Standard	Interpretation
No consensus on the most appropriate goals to define for population-based RGCS	Standard 5.1 Guidelines should be developed around explicitly defined clinical or public health questions	In the context of RGCS, the evolution from targeted screening to population-based screening has created a fundamental shift in how one must think about the goals of RGCS and how these are informed by clinical or public health paradigms.[35] Currently, there is dichotomy in the goals attributed to RGCS. Reduction of disability or disease incidence from a public health perspective is a common goal based historically on targeted screening offers. This contrasts with facilitating reproductive autonomy and informed reproductive decision-making as a key goal that is perceived to be more appropriate from an ethical perspective. No consensus currently exists on the most appropriate goals for RGCS. Therefore, current practice recommendations that encourage the offer of RGCS to all women planning a pregnancy or in their first trimester do not satisfy the NHMRC Standard 5.1 as the goals of RGCS are currently not explicitly understood or agreed upon.
No consensus on appropriate outcomes	Standard 5.2 Guidelines should address outcomes that are relevant to the guideline's expected end users	There is currently no consensus on the outcomes that are most appropriate to assess to capture the benefit of RGCS, and there is marked variability in the outcomes assessed across the literature. Standard 5.2 cannot be fulfilled until a clearer understanding of meaningful outcomes is achieved. Evidence regarding this is discussed in Chapter 3.
Lack of involvement of patients in the selection of research outcomes	Standard 5.3 Guidelines should clearly define the outcomes considered to be important to the person/s who will be affected by the decision and prioritise these outcomes.	There is a lack of patient involvement in the research design process, including defining and selecting outcomes that can accurately capture the patient experience and benefits/harms of RGCS. Standard 5.3 necessitates a clearer understanding of the outcomes that are relevant to the setting in which the guideline is being developed than currently exists for RGCS. Evidence regarding this is discussed in Chapter 3.

Lack of synthesised evidence of benefits from systematic reviews	Standard 6.1 Guidelines should be informed by well-conducted systematic reviews	Systematic reviews that demonstrate conclusively the benefits of RGCS are currently lacking. A Cochrane systematic review aimed at evaluating RGCS for thalassaemia, sickle cell disease, cystic fibrosis and Tay-Sachs disease identified no studies for inclusion because of the strict inclusion criteria required of randomised controlled trials (RCTs).[50] This review recommended consideration of non-RCT studies and inclusion of expanded carrier screening offers when the review is next revised as a pragmatic approach to ensuring that systematic review evidence would be available to inform practice recommendations in the future. Standard 6.1 cannot currently be fulfilled because of the need for more systematic reviews.
It is implausible for a guideline panel to consider in full a large body of evidence	Standard 6.2 Guidelines should consider the body of evidence for each outcome (including the quality of that evidence) and other factors that influence the process of making recommendations, including benefits and harms, values and preferences, resource use and acceptability	Given the heterogenous approaches taken when evaluating RGCS in the current literature, it is not feasible for guideline panels to review the evidence sufficiently for all relevant outcomes. Systematic reviews would reduce any bias introduced by the selection of studies that can be considered within the resources of the guideline panel.

The NHMRC standards recognise that focusing on the right outcomes is needed to ensure that guidelines across all topics address the needs of stakeholders, including the target population. Considerable research waste can be avoided by engaging with consumers to ensure an accurate understanding of meaningful outcomes and ensuring that these are addressed when developing practice recommendations.[51] These standards also recognise that practice recommendations should be based on the best available evidence.[42] An audit of guidelines in 2014 showed that only 7% included a replicable description of the evidence review and only 17% clearly linked their recommendations to specific evidence.[52] This is a systemic issue within guideline development and being aware of such limitations is important to the interpretation of practice recommendations.

As seen in Table 2, there is a lack of clear evidence available to inform practice recommendations of RGCS. When evidence-based recommendations are not able to be achieved, a guideline panel can issue consensus-based recommendations if there is sufficient agreement. When these are issued, there should be an acknowledgement of the desirability of developing evidence-based recommendations and consideration of how this can be accommodated in the future.[41] The aforementioned SOGC-CCMG, ACOG and RANZCOG practice recommendations supporting the widespread offer of RGCS are consensus-based recommendations. There is increasing recognition that consensus-based recommendations are a weak foundation for informing clinical practice and that the rigor of evidence-based practice recommendations should be the aim of guideline development.[53]

The limitations in current practice recommendations indicate that more research is needed to work towards evidence-based practice recommendations that can inform the implementation of population-based RGCS. With a few exceptions, universally accessible RGCS is currently available only through commercial offers that incur out-of-pocket costs to patients. This has resulted in uptake in largely white, high socio-economic and highly educated populations. This means that the research evidence may be limited to this demographic and that this evidence base lacks generalisability to more diverse populations. Agreement on the goals of RGCS as it transitions to a population-based screening offer and standardisation of the outcomes that can meaningfully capture its benefits are key areas for future research and are considered throughout this thesis.

1.6 Introduction to core outcome set development

This section provides a brief introduction to core outcome set (COS), the potential benefits in the setting of RGCS and the professional organisations relevant to informing the methodology for COS development.

1.6.1 Addressing systemic issues in outcomes research

As with other areas of medicine, one of the aims of research in the field of genetics is to understand the benefits and harms of genetic testing as a health intervention. This aim is most often achieved by measuring the impact of a genetic test on patient outcomes when it is used in clinical practice; however, this is acknowledged to be challenging.[54,55] The literature focuses on demonstrating the effectiveness of clinical genetics services, genetic counselling and genetic testing, and systematic reviews have demonstrated a modest positive impact.[12,15,16,56-59] A problem that has arisen frequently in the genetics literature is comparability across studies because of heterogeneity in the choice of outcomes and method of measurement. Often studies measure the same or similar concepts, such as psychological impact, but vary in the specific outcome they report within this broad domain, use different measurement tools and measure the outcome at variable time points. The presence of outcome heterogeneity hinders the ability to compare and contrast directly the results of different studies and to combine these results in a meta-analysis. This issue has been highlighted in research and commentary on the outcomes of genetic testing and genetic counselling, and is becoming a focus of many discussions within the field.[15,59]

Another issue noted in genetics research is the propensity for observational study designs because of the challenges of including a comparison group in the clinical setting. Few studies on RGCS are experimental in design, and only a handful of RCTs have been published. Observational study designs have a lower standard of methodological rigor and a number of potential problems that may lead to biasing of results.[60] One such issue is that there is no requirement or tendency to publish a protocol outlining the outcomes that will be measured. This introduces a risk of reporting bias because of the lack of accountability for publishing all outcomes, regardless of whether they support the author's position or reach statistical significance. There is also a great deal of variability in the inclusion of patient-reported outcomes, which are important for ensuring that the results of the research are relevant to patients. A few systematic reviews have been conducted in the field of RGCS; these focus mainly on carrier screening for specific conditions. The

reviews that addressed data analysis and risk of bias in their methods, identified issues with outcome heterogeneity, study design and overall quality of evidence, whereas others that did not specifically address these issues performed narrative syntheses, which indicates that a meta-analysis was not possible with the available data.[58,61-64]

This thesis proposes the development of a core outcome set (COS) for RGCS. A COS is defined as an agreed minimum set of outcomes that should be measured and reported in all clinical trials in specific areas of health or health care.[65] COS are also recognised to be appropriate for use across other study designs, such as observational studies, and for clinical auditing purposes. The development of a COS applies a rigorous approach to defining outcomes that are relevant to all key stakeholders of a health intervention. COS are often developed for a specific population, such as those with a particular genetic condition, and can be used to evaluate interventions that are applied to that population. As RGCS is a population-based screening offer available to all women planning a pregnancy or in their first trimester, the focus of this COS will be on the genetic testing intervention itself.

Development of a COS aims to minimise the heterogeneity in outcomes that are measured by different researchers and, as a result, maximises the ability to compare and combine studies in meta-analyses or other data synthesis approaches. Defining a COS also reduces the likelihood of reporting bias by ensuring that, at the very least, the core outcomes are reported in all studies on an intervention. The incorporation of individuals who have had RGCS, clinicians involved in their care and researchers and policy-makers who guide practice in this area, in the development of this COS will ensure that outcomes are relevant to all stakeholders.

The Core Outcome DEvelopment in Carrier Screening (CODECS) study applied the methodology outlined by the COMET (Core Outcomes Measures in Effectiveness Trials) Initiative to develop a COS for RGCS. This COS is intended to be used across all study designs and is also applicable to clinical audits and systematic reviews on RGCS. To my knowledge, this study is the first example of a COS aimed at standardising the reporting of outcomes in studies of a genetic testing intervention.

1.6.2 The Core Outcome Measures in Effectiveness Trials (COMET) initiative

The Core Outcome Measures in Effectiveness Trials (COMET) initiative "aims to bring together people interested in the development, reporting and promotion of COS, derived using rigorous consensus methods".[66] The COMET initiative supports a database of all

current planned and ongoing COS studies.[67] The methodology used throughout this thesis is informed by the COMET handbook[65], and by published guidance regarding protocol planning[68], development[69] and reporting[70] of COS. The key steps of the COS development process, as defined by the COMET initiative, are summarised in Figure 1.

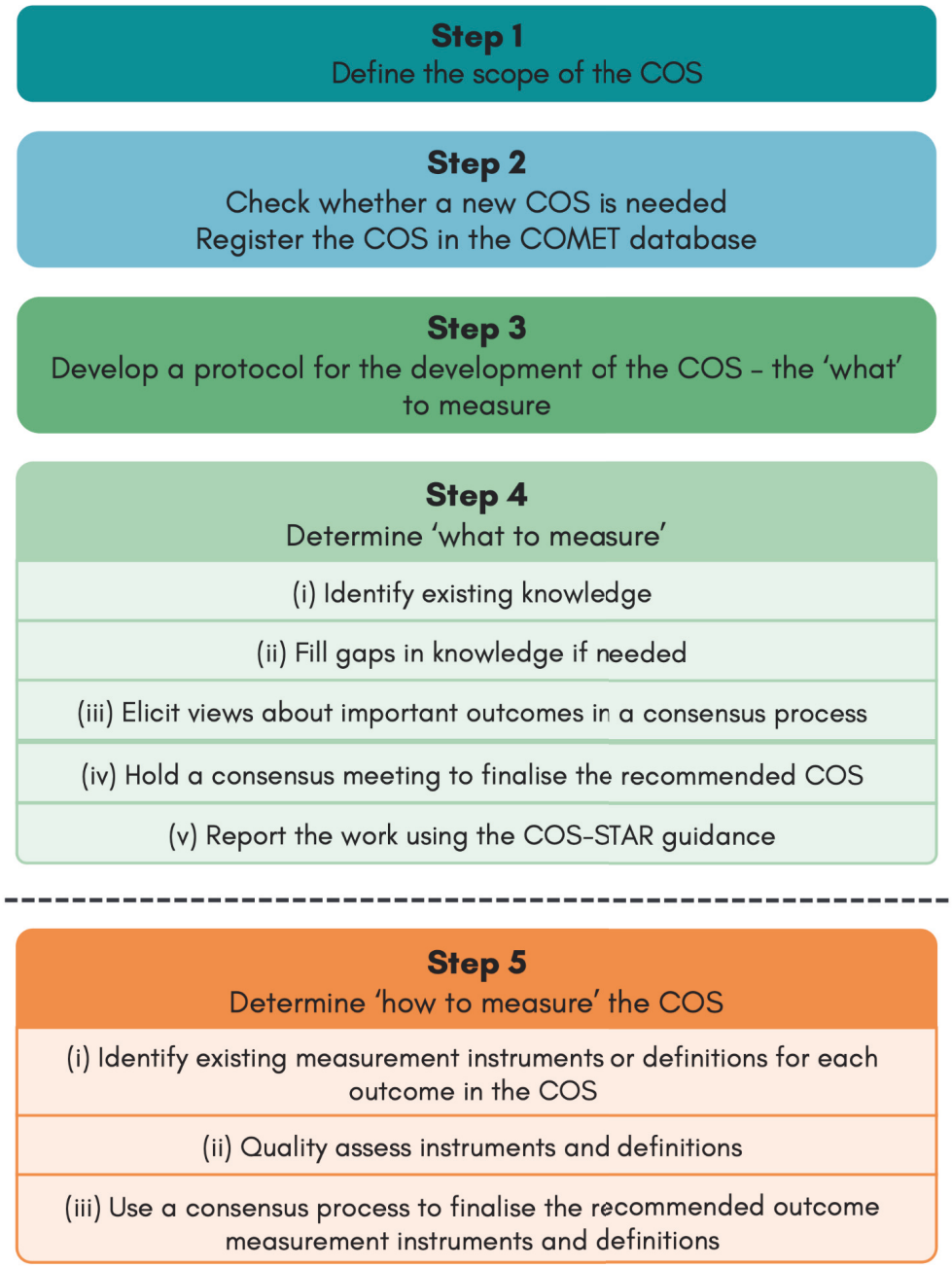

Figure 1: Overview of the steps involved in developing a COS.
Adapted from the COMET Handbook[65]

To facilitate the classification of outcomes identified during COS development into overarching outcome domains that correspond to key aspects of health care, a taxonomy was developed for use throughout this thesis, expanding on an existing taxonomy from the COMET initiative.[71] This taxonomy classifies outcomes into five core areas: (1) mortality/survival, (2) physiological/clinical, (3) life impact, (4) resource use, and (5) adverse events/effects. These are referred to as COMET core areas throughout this thesis. An increasingly granular tier of outcome domains is defined within each core area, and these are referred to as COMET outcome domains. Developers of COS are encouraged to define their own more granular tier for their specific study to capture the outcomes relevant to their specialty; as such, the relevant outcome domains included in this thesis have been subdivided into a tier of domains that can capture the level of detail appropriate to the genetic setting and are referred to as CODECS outcome domains. The outcomes identified throughout the course of this thesis are presented using these three tiers (COMET core area, COMET outcome domains, and CODECS outcome domains).

1.7 Overview of the thesis

In this section, I provide an overview of the chapter structure of this thesis and highlight the steps of the CODECS study completed within the scope of this thesis. I define the aims and the guiding principles that have governed the conduct of the CODECS study.

1.7.1 Chapter structure

An overview of the chapter structure of this thesis is presented in Figure 2. As this is a thesis by compilation, Chapters 2-5 present accepted manuscripts from peer-reviewed journals and contain some repetition necessary for the standalone manuscripts. For instance, the concepts of RGCS and COS and some methods, including the COMET taxonomy, are described in each chapter.

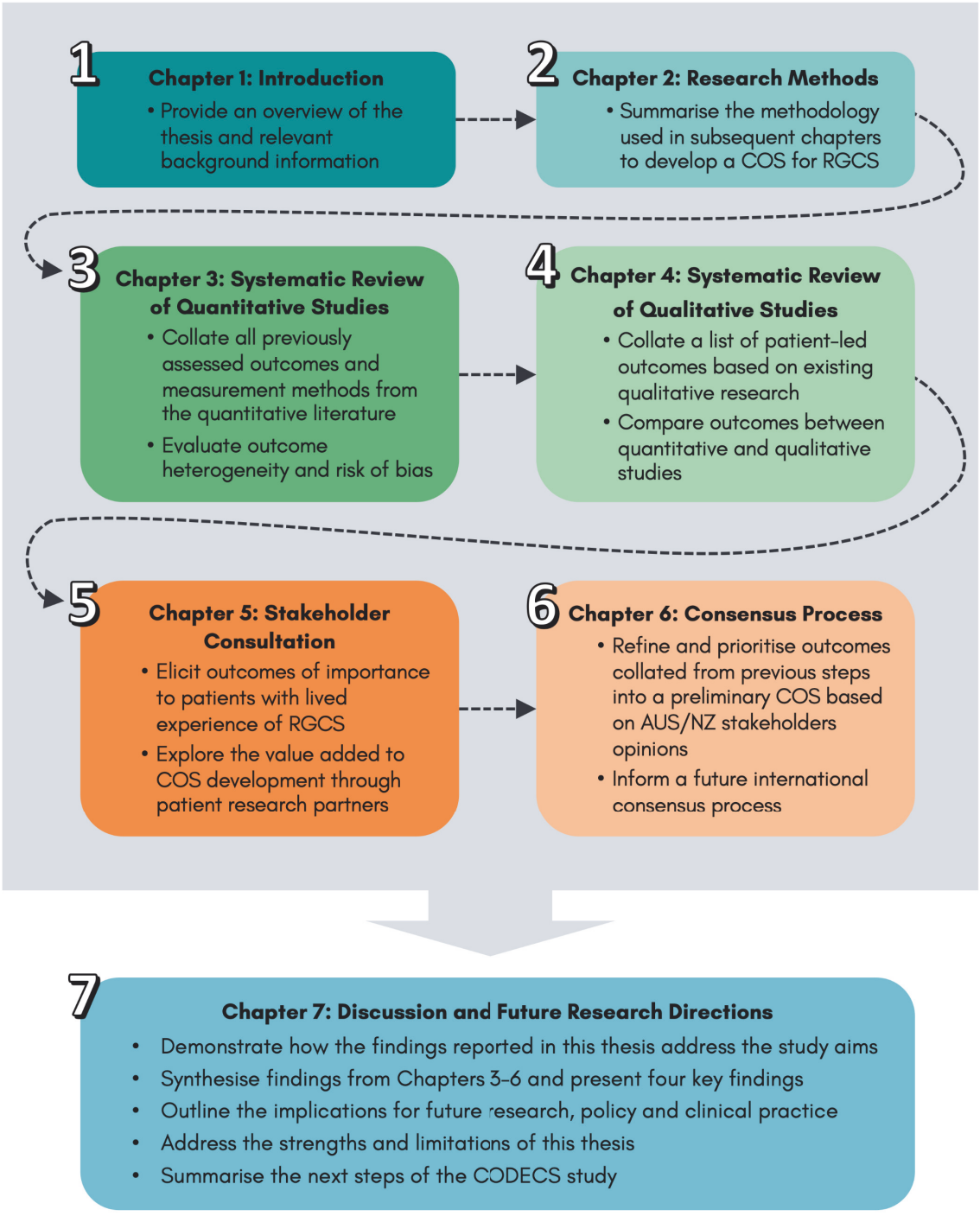

Figure 2: Diagrammatic overview of the thesis with aims

1.7.2 Steps of the CODECS study presented in this thesis

Where referred to, the CODECS Study encompasses the entire development process planned to culminate in the definition of a COS for RGCS. This thesis will present steps 1-4.iii as described in Figure 1. The next steps needed to define a final COS are discussed in Chapter 7 (Discussion).

Reasons informing the scope of this thesis

During initial planning, the intention was to undertake steps 1 through 4 as outlined in Figure 1 in full by including an international Delphi survey and consensus meeting, and reporting of a COS within the scope of this thesis. For practical reasons, this was not possible, and the planned scope was adjusted throughout the PhD and agreed upon by the study management group to ensure the planned study was feasible for completion in the time allotted for this thesis.

The first influencing factor was the planned systematic review of the literature. At the start of my studies and when gathering of relevant publications, it became apparent that this would be a more extensive undertaking than initially thought. The extent of quantitative and qualitative studies available necessitated that the review be split into two and conducted sequentially. Limited resources were available for duplicate screening of publications, a crucial step for the rigor of a systematic review, and title, abstract and full-text screening exceeded the time initially allowed. Similarly, data extraction and synthesis were made more complex by the volume of data gathered. Given the time needed to complete these systematic reviews, undertaking an international consensus process was no longer feasible, and alternatives were discussed with the study management group at monthly supervision meetings.

The second influencing factor was the onset of the COVID pandemic in March 2020 as the ethics application for the final two studies, qualitative stakeholder consultations and the consensus process, was compiled. COVID caused significant disruptions worldwide and necessitated transition to a work from home model. Accessing equipment for a work from home set up, accessing resources online and establishing remote modes of communication and supervision all required adjustment to the thesis scope. As it became apparent that these disruptions would not be short-term and in light of the delays already caused by the systematic review process, it was necessary to adjust the planning and reduce the scope for this thesis to completed by the expected work submission date.

Chapter 2 presents the published protocol for the CODECS study. The methods outlined represent the intention for development of a full COS and, although only part of the results are presented in this thesis, the CODECS study is ongoing. Changes to the protocol to reflect what is reported in this thesis are indicated in Section 2.5 at the end of Chapter 2 and are discussed where relevant throughout the thesis.

1.7.3 Aims of the CODECS study

The primary aims of the CODECS study were as follows.

Aim 1: To establish an evidence base to support the development of a core outcome set for reproductive genetic carrier screening. This aim is addressed in Chapter 3.

Aim 2: To explore the patient experience of reproductive genetic carrier screening and engage in a co-design process to understand the outcomes of importance to patients. This aim is addressed in Chapters 4 and 5.

Aim 3: To conduct a consensus process to refine and prioritise the outcomes identified throughout the CODECS study and define a core outcome set for use in all future studies of RGCS. This aim is addressed in Chapter 6.

Because the scope of work in this thesis was reduced, the third aim was amended to:

Aim 3: To understand the level of consensus on the core outcomes that should be measured by all future studies of RGCS. This aim is addressed in Chapter 6.

1.7.4 Guiding principles of the CODECS study

The principles outlined below have governed all study design and methodological choices for the CODECS study.

Principle 1: To recognise existing research efforts, we will incorporate the body of existing literature into our work to ensure that the efforts of previous studies are considered and valued.

Principle 2: To recognise patients as the experts in their own needs and experience, we will ensure that the patient perspective is considered throughout the study and that outcomes of importance to patients are incorporated in the core outcome set.

Principle 3: To recognise the international relevance of RGCS, we will strive to maximise the generalisability of the core outcome set by incorporating international perspectives in each phase of the study.

1.7.5 Setting

The CODECS study was conducted through the Graduate School of Health (GSH), University of Technology Sydney (UTS) and, where appropriate, individual studies were approved by the UTS Human Research Ethics Committee (HREC). All research participants participated in the studies remotely.

1.7.6 Consultation

The CODECS study, and the individual projects that compose it, were developed in consultation with the Study Management Group (SMG). The SMG comprised my primary supervisor Dr Chris Jacobs, my secondary supervisors A/Prof Alison McEwen and Prof Toby Newton-John, and me. A Study Advisory Group (SAG) was also convened and comprised a genetic counsellor with expertise in offering RGCS; a clinical geneticist with expertise in offering, conducting research and developing practice recommendations for RGCS; an expert in COS development and methodology; a patient representative with lived experience of undertaking RGCS; and a patient advocate representative from a support organisation. The SAG members were consulted for advice specific to their expertise throughout the development and conduct of the CODECS study. Advice was sought from the COMET Initiative during the conceptualisation stage of the CODECS study to gather appropriate resources and inform methodological choices. During the conceptualisation of each study, methodological choices and decisions were presented and discussed at a monthly UTS Genetic Counselling Research Group seminar attended by academic and teaching staff and other PhD candidates from UTS and other universities. Studies were also presented at the UTS GSH research student forum annually.

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Chapter 2: Research methods

2.1 Chapter overview

This chapter provides a detailed description of all planned research methods within the CODECS study and is structured per the corresponding published protocol, except for the background section, which is presented in Chapter 1. This protocol is written in the future tense and is representative of the intent of the CODECS study in full. As outlined in Chapter 1, only a portion of the full study is presented in this thesis, and changes to this protocol that are relevant to future chapters are summarised in Section 2.5.

> Richardson E, McEwen A, Newton-John T, Manera K, Jacobs C. The Core Outcome DEvelopment for Carrier Screening (CODECS) study: protocol for development of a core outcome set. *Trials*. Jul 22 2021;22(1):480. doi: https://doi.org/10.1186/s13063-021-05439-7

2.2 Abstract

Background: Reproductive genetic carrier screening is a type of genetic testing available to those planning a pregnancy, or during their first trimester, to understand their risk of having a child with a severe genetic condition. There is a lack of consensus for 'what to measure' in studies on this intervention, leading to heterogeneity in choice of outcomes and methods of measurement. Such outcome heterogeneity has implications for the quality and comparability of these studies and has led to a lack of robust research evidence in the literature to inform policy and decision-making around the offer of this screening. As reproductive genetic carrier screening becomes increasingly accessible within the general population, it is timely to investigate the outcomes of this intervention.

Objectives: The development of a core outcome set is an established methodology to address issues with outcome heterogeneity in research. We aim to develop a core outcome set for reproductive genetic carrier screening to clarify and standardise outcomes for research and practice.

Methods: In accordance with guidance from the COMET (Core Outcome Measures in Effectiveness Trials) Initiative, this study will consist of five steps: i) A systematic review of quantitative studies, using narrative synthesis to identify previously reported outcomes,

their definitions, and methods of measurement ii) A systematic review of qualitative studies using content analysis to identify excerpts related to patient experience and perspectives that can be interpreted as outcomes iii) Focus groups and/or semi-structured interviews with patients who have undertaken reproductive genetic carrier screening to identify outcomes of importance to them and understand the reason why these outcomes are prioritised iv) Delphi survey of key stakeholders, including patients, clinicians, and researchers, to refine and prioritise the list of outcomes generated from the previous steps v) A virtual consensus meeting with a purposive sample of key stakeholders to finalise the core outcome set for reporting.

Discussion: This protocol outlines the core outcome set development process and its novel application in the setting of genetic testing. This core outcome set will support the standardisation of outcome reporting in reproductive carrier screening research and contribute to an evolving literature on outcomes to evaluate genetic testing and genetic counselling as health interventions.

COMET core outcome set registration: http://www.comet-initiative.org/Studies/Details/1381

Keywords: Core outcome set, Reproductive genetic carrier screening, Genetic counselling, Patient-reported outcomes, Qualitative research, Delphi Survey, Outcome reporting

2.3 Methods/design

2.3.1 Scope

The methodology defined by the COMET (Core Outcomes Measures in Effectiveness Trials) Initiative and the Core Outcome Set-STAndardised Protocol Items (COS-STAP) Statement will inform this protocol.[1,2] The COMET database was searched to confirm that there were no overlapping projects and the CODECS study subsequently registered (http://www.comet-initiative.org/Studies/Details/1381). The PICO framework is recommended by the COMET initiative for defining the scope of a core outcome development study, using the first three elements of population, intervention, and comparator.[3] The population that this COS is being developed for incorporates any individual or couple that is offered genetic carrier screening to inform their current or

future reproductive decisions. This may be offered as population screening in increased risk populations as well as the general population and includes school, community, preconception, and prenatal programs. This COS is not intended to cover cascade carrier screening in family members following the diagnosis of a genetic disease in a family member.

The definition of the intervention includes RGCS via targeted single-gene or small gene panels, through to pan-ethnic expanded carrier screening panels and virtual panels from whole-genome sequencing. The intervention encompasses pre-test genetic counselling, genetic testing, and post-test results management. Molecular genetic testing methodologies are the predominant laboratory method of carrier screening currently. However, some programs do remain reliant on biochemical methods to triage access to molecular genetic panels. An example of this is haemoglobinopathies screening programs, which use results of mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH) ± anaemia, to triage which individuals will be screened using molecular methods. This COS is intended to be applicable to molecular and combined biochemical/molecular methods. A comparator is not expected to be appropriate for most RGCS programs. However where appropriate, we will include comparators such as control populations (no RGCS testing) and targeted versus expanded interventions (single gene or small panels compared to expanded panels). This COS is intended to be applicable to all population-based RGCS scenarios and is being developed to take into account the significant variability in screening approaches used internationally.

This COS is being developed for use in research on RGCS, as well as in clinical practice. The majority of research in this area involves observational study designs assessing the impact of RGCS after it has already been implemented into clinical practice, and it is only recently that there has been a shift in the literature towards more rigorous study methodologies using randomised controlled designs. Therefore, it was decided that separating out the research and clinical contexts was not possible for this COS.

The CODECS study involves five steps: a systematic review of quantitative literature, a systematic review of qualitative literature, semi-structured focus groups/interviews with patient stakeholders, an international online Delphi survey, and a virtual consensus meeting (Figure 3).

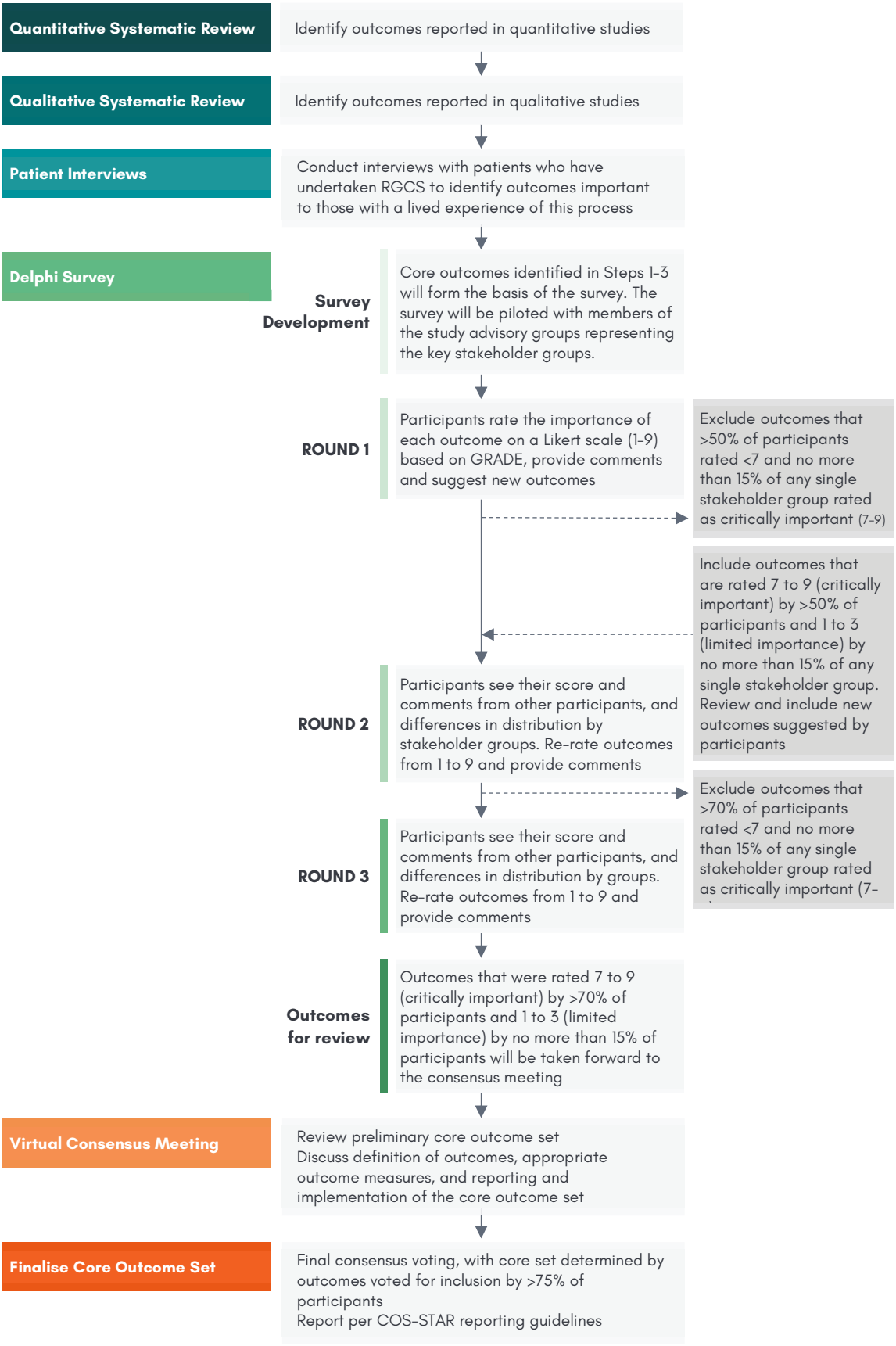

Figure 3: Study overview diagram

2.3.2 Step I – Systematic review of outcomes reported in quantitative studies on reproductive genetic carrier screening

A systematic review of the literature will be conducted to identify outcomes and their method of measurement in studies evaluating an offer of RGCS. These will form the basis of the preliminary list of outcomes that will be reviewed and refined during the consensus process. The full protocol for this systematic review is published on the international prospective register of systematic reviews, PROSPERO (CRD42019140793).

Study selection

MEDLINE, CINAHL, PsycINFO, and EMBASE will be searched for quantitative, qualitative, and mixed-methods studies. The quantitative and qualitative studies identified will be reviewed separately to account for the different approaches needed to extract the outcomes. Step I will include studies that are solely quantitative, or for mixed methods studies, the portion of quantitative data. A percentage of title and abstract screening will be performed independently by two reviewers until inter-rater reliability of >85% is achieved, after which the remainder will be screened by ER only due to resource limitations. The full-text screening will be similarly performed. Any disagreement on the eligibility of studies will be resolved through discussion with a third reviewer.

All peer-reviewed published studies where reproductive genetic carrier screening has been offered as a health intervention will be eligible for inclusion. Studies that are primarily evaluating laboratory test methodology, are not primary research, where the context of testing is not primarily related to RGCS (for example, newborn screening, cascade carrier screening), or that are not available in English, will be excluded.

Data extraction

Outcomes will be extracted from eligible studies from the last five years to form a preliminary list; the review will then proceed to the previous five years and compare outcomes to the preliminary list. If no additional outcomes are identified, the review will be considered complete after this 10-year period; however further cycles will be conducted if additional outcomes continue to be identified. This methodology is per the guidance of the COMET Handbook, suitable for situations where the size of the review would be unmanageable if conducted in full.[2] A guideline for data extraction has been developed and will be piloted with two independent reviewers for 20% of studies. Outcomes, and where supplied, their definition, method of measurement and time point,

will be extracted verbatim from studies using NVivo software. The primary outcome, if specified, will be noted. In addition, study type, target population, intervention type, screening approach, and other basic study characteristics will be extracted.

Quality assessment

The quality of the included studies will be scored using the QualSyst tool by the primary reviewer (ER).[4] In the context of a systematic review of outcomes where the aim is to determine all published outcomes regardless of study quality, the assessment of bias will not be used as grounds for exclusion but rather to give an overall evaluation of the quality of studies within the RGCS literature.

Analysis and presentation of results

A narrative synthesis will be conducted on data extracted from quantitative studies, with outcomes to be grouped within domains and mapped to the COMET taxonomy.[5,6] The domains will be reviewed and discussed by the CODECS study management group. The number of different outcomes (including the method of measurement and time points) and the number of studies that assessed each outcome will be evaluated. Subgroup analyses will be considered to identify outcomes that may be specific to targeted and expanded carrier screening approaches.

2.3.3 Step II: Systematic review of outcomes reported in qualitative studies on reproductive genetic carrier screening

The inclusion of patient perspectives is considered a minimum standard of the COS development process in accordance with the Core Outcome Set-STAndards for Development (COS-STAD).[7] The COMET handbook suggests that the preliminary list of outcomes generated by a systematic review of the quantitative literature may be supplemented with additional domains derived from a review of the qualitative literature if time and resources allow.[2] We will apply the methodology developed by Gorst et al. to extract outcomes of importance to patients from the qualitative literature on RGCS.[8] We will compare the extracted outcomes identified from the qualitative literature with those identified from the quantitative literature. These outcomes will be used to identify gaps in knowledge or representation of patient groups to guide focus groups/interviews in Step 3.

Study selection

The initial steps of the systematic review will be conducted in the same manner as the quantitative studies described above, diverging at the point of data extraction. Eligible studies will be those that utilise qualitative methodology or mixed methods studies involving a qualitative component.

Data extraction

It is not anticipated that any existing studies will have conducted qualitative research specifically for the purpose of identifying outcomes. Therefore, our approach to data extraction will be deductive, taking excerpts verbatim from the qualitative literature and deducing the outcome that they represent. Excerpts will be any text relating to how patients felt or were impacted by their experience of undertaking RGCS, including quotations and author's interpretation of themes. Each relevant excerpt will be extracted as a node using NVivo software by the primary reviewer (ER) and checked by a second reviewer (CJ) to ensure that all relevant text excerpts have been extracted. Both reviewers will then independently interpret outcomes from 20% of studies and check these for agreement. A coding guideline will be developed and used by the primary reviewer (ER) to interpret the remaining excerpts.

Quality Assessment

The quality of the included studies will be scored as described above for quantitative studies.

Analysis and presentation of results

We will draw on content analysis to conduct a narrative synthesis of the data from eligible studies.[6] This method will allow us to convert qualitative findings into frequency counts that reflect the outcomes relevant to patients experience of RGCS. The outcomes captured in this way will be compared to those identified in the quantitative literature, with new outcomes indicating potential new areas for investigation. Outcomes will be grouped within domains and mapped to the COMET taxonomy as above. Each text excerpt and its deduced outcome will be independently categorised into the taxonomy by two reviewers (ER and CJ). All categorisations will be discussed until 100% agreement is reached, with reference back to the original article for context as needed. Some outcomes are expected to be relevant to multiple domains within the taxonomy, and

where this occurs, they will be categorised under two domains as recommended in the taxonomy guidance.[5]

2.3.4 Step III: Patient focus groups and/or semi-structured interviews

We will conduct primary qualitative research with patients who have undertaken RGCS to identify outcomes important to those with a lived experience of this process. We will give participants a choice of attending a focus group or one-on-one semi-structured interview. Focus groups are a valuable way to encourage participant interaction and enrich the sharing of their experiences; however there are a number of factors that may influence the appropriateness of conducting focus groups.[9] It is possible that recruitment may be limited by factors related to the sensitivity of the research topic, in particular amongst participants that fall into the increased risk group and may feel uncomfortable relaying their experience in a group setting. Therefore, the option of one-on-one interviews will also be available and decided upon once recruitment is underway.

Participants and recruitment

We will recruit individuals or couples who have had RGCS in order to inform their reproductive decisions. Participants groups will be defined by two characteristics; their level of risk prior to RGCS (a priori) and their level of risk following results (a posteriori). A priori risk will be either average or increased. Average a priori risk will be defined as *the participant having no existing health concerns or family history to indicate an increased risk of being a carrier*. Increased a priori risk will be defined as *the participant having an existing factor such as ethnicity with a known increased frequency of carriers or a known family of a genetic condition that is included in the screening*. There are a number of potential outcomes of RGCS; however, a posteriori risk will be grouped into either low or increased reproductive risk. Low reproductive risk results are defined as those where neither member of a reproductive couple are found to be carriers of the same genetic condition, or where one member of a reproductive couple is found to be a carrier of an autosomal recessively inherited genetic condition but their reproductive partner is not a carrier of the same condition. Increased reproductive risk is defined as those where both members of a reproductive couple are found to be carriers of the same autosomal recessively inherited genetic conditions, or where the female reproductive partner is found to be a carrier of an X-linked genetic condition. We will aim to recruit 30 participants, with equal representation from each group.

To recruit an international and diverse sample with a range of experiences, we will circulate an expression of interest to participate in the research through a number of social media channels and parenting forums. Respondents who follow the link will be directed to an online survey on the Qualtrics platform to receive more information about the research and fill out basic demographic and screening questions to confirm their eligibility.[10] Eligible participants will be from countries that score >50 on the corruption perceptions index, indicating that they are not vulnerable populations.[11]

Data collection

Focus groups/interviews will be conducted using Zoom, an online audio- and video-conferencing platform.[12] Recent research has indicated the viability of Zoom as a tool for the collection of qualitative data due to its ease of use, cost-effectiveness, data management, and security features.[13] Focus groups will be approximately 90 minutes, depending on the number of participants. One-on-one interviews will be up to 60 minutes in duration. An online platform has been chosen to facilitate international participation and reduce the inconvenience of travelling for participants. Focus groups/interviews will be audio- and video-recorded and transcribed verbatim. The focus group/interview schedule will begin with open questions to elicit patient experiences, after which more specific questions related to outcomes will be informed from the list of outcome domains generated from the systematic review steps above. Our data collection will draw on grounded theory, with data collection and analysis occurring concurrently and utilising constant comparison to refine data collection as the study progresses. [14]

Data analysis

Using thematic analysis, the transcripts will be reviewed line by line and inductively coded to identify concepts.[15] Similar concepts will be grouped into themes and corresponding subthemes. These concepts/themes will reflect the perspectives, beliefs, and values of participants in regards to outcomes of reproductive carrier screening. To ensure that the complete range and depth of the data are included, at least two investigators will be involved in coding the data. Data collection will continue until data saturation is reached (the point at which no new themes are identified).

2.3.5 Step IV: Delphi survey

We will follow published principles of applying the Delphi process in the context of COS development.[16] This process will utilise a sequential, two to three round online survey with an internationally representative sampling of key stakeholders in the field.

Developing the survey

The preliminary list of outcomes generated from the previous steps will be reviewed by the research team to form the basis of the Delphi survey. Lay language summaries will be developed and presented together with the medical definitions to facilitate the participation of patients in this step of the COS development process. The Delphi survey will be generated using Qualtrics software and piloted with the study advisory group. Feedback will be incorporated into the survey structure, definitions and lay-language summaries, and overall usability of the survey.

Participants and recruitment

Five key stakeholder groups with current or recent personal, clinical, research, or policy experience of RGCS will be targeted for the Delphi survey; patients (including both carriers and non-carriers identified through targeted or expanded screening), genetic health professionals (genetic counsellors and clinical geneticists), non-genetics health professionals (obstetrician/gynaecologists, midwives, general practitioners), and policy-makers.

No recommendations currently exist regarding sample size for a Delphi survey, with wide variability in the number of participants across Delphi surveys for COS development.[17] Decisions regarding sample size are based on the area of practice and feasibility of recruiting sufficient representation from each stakeholder group. As this is the first COS that we are aware of in the setting of genetic testing, we do not have a guide for how many stakeholders may be willing to participate in this process. We have adopted the approach of COS developers in the obstetric setting.[18] Equal representation of patient and professional perspectives is desirable; as such, we will aim to recruit at a minimum 50 patient participants and 50 participants from other professional stakeholder groups to the first round of the Delphi survey. In recognising natural rates of attrition in subsequent rounds, this number should allow sufficient representation through the three rounds of the Delphi process.

Our recruitment strategy incorporates diverse methods of identifying and recruiting participants to account for the range of key stakeholders that we are aiming to include. Expressions of interest to participate will be distributed through various channels: 1) patient participants from focus groups/interviews will be invited to participate in the Delphi process. We will also recruit through social media to reach our goal of 50 total patient participants; 2) researchers in the field will be purposively sampled based on first and last authors of papers included in our systematic reviews; 3) genetic and non-genetic health professionals will be purposively sampled based on professional networks of the research team and members lists of relevant professional organisations; 4) policy-makers will be purposively sampled from listed committee members on major practice recommendations related to RGCS. All participants will be encouraged to snowball information about the study to their networks to ensure a broad range of participants and experiences are captured. Participants who respond to expressions of interest through any of the above channels will be directed to an online survey on the Qualtrics platform to receive more information about the research and fill out basic demographic and screening questions to confirm their eligibility. Once eligibility is confirmed, they will receive the link to the Delphi survey, where they will be required to electronically indicate their consent before proceeding to the consensus questions. During the Delphi survey, recruitment may be targeted to groups that are under-represented to ensure balanced representation.

Data collection

In round 1, participants will be asked to rate each outcome on a nine-point Likert scale based on the degree of importance as recommended by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group.[19] Rating 1 to 3 will be interpreted as "limited importance"; 4 to 6 as "important, but not critical"; and 7 to 9 as "critical importance." An option of "unsure" will also be available. The sequence of questions will be randomised to minimise ordering bias. For each outcome, a free text box will be available for participants to provide feedback or comments. New outcomes can be suggested by participants at the end of round 1 and will be reviewed by the research team to determine if they are unique and not overlapping, wholly or partially, with an existing outcome. Those that are deemed to be suitable will be carried over to round 2.

There is a lack of agreement on the definition of consensus to be used when deciding which outcomes to include in the second round of a Delphi survey, and a wide range of thresholds have been utilised in COS development. Per the guidance in the COMET handbook, using less stringent criteria in earlier rounds and considering responses from individual stakeholder groups minimises the likelihood that outcomes that may have been rated higher in subsequent rounds after receiving feedback are not dropped too soon in the Delphi process.[2] We will adopt the definition utilised in a recent COS developed for surgery in oesophageal cancer, whereby criteria for inclusion in round 2 will be any outcomes that are rated 7 to 9 (critically important) by >50% of participants and 1 to 3 (limited importance) by no more than 15% of any single stakeholder group.[20] Results will be presented graphically to participants at the time of the second round of the survey along with their rating of each outcome and any representative comments provided by participants that indicate their reasoning. This will allow participants to compare their ratings to other participants and consider whether they would change their rating in the next round. Participants will then be directed to re-rate the outcomes that have been carried over from the first round, with a free text box once again available for them to explain their rating or respond to comments from other participants from round 1. More stringent criteria for consensus will be applied to determine if there is a need for a third round of the Delphi survey, with outcomes that are rated 7 to 9 (critically important) by >70% of participants and 1 to 3 (limited importance) by no more than 15% of any single stakeholder group.

A third round of the Delphi survey will be conducted if the number of outcomes remaining after the second round is too high to reasonably discuss at a consensus meeting. Criteria for inclusion may need to be adjusted at the time of the Delphi if sufficient reduction in outcomes is not being achieved, changes to which will be reported alongside the results of the Delphi survey. Following the final round of the Delphi survey (whether that is the second or third), outcomes that were rated 7 to 9 (critically important) by >70% of participants and 1 to 3 (limited importance) by no more than 15% of participants will be taken forward to the consensus meeting for consideration of inclusion in the final COS.

Each round of the survey will be open for a minimum of four weeks to provide participants with sufficient time to complete it. A maximum of 3 reminders will be sent to participants when two-weeks, one-week, and one-day are remaining to complete the

survey. At the end of round 2 of the Delphi survey, participants will be asked to indicate if they are interested in participating in the final consensus meeting.

Data analysis

We will summarise the overall distribution in ratings for outcomes across the rounds of the Delphi survey and the points at which outcomes were excluded from consideration. The mean and median will be calculated for each outcome. Data will be analysed in sub-groups to allow comparison between prioritisation of outcomes between health consumer participants and other stakeholder participants, and also between different subsets of the other stakeholder groups (for example, genetics health professionals versus non-genetic health professionals).

2.3.6 Step V: Consensus meeting

We will host a virtual consensus meeting using Zoom. The purpose of this meeting will be to review the findings from steps 1-4 and discuss the outcomes for inclusion in an agreed-upon COS. Methods of measurement, implementation, and directions for further research will also be discussed if time allows.

Participants and recruitment

From the participants that complete the Delphi survey, a maximum of 15 (two to three from each participant group) will be purposively selected from those that have indicated an interest in participating in the final virtual consensus meeting, ensuring equal representation across stakeholder groups. We may consider contacting Delphi participants that did not express interest at the conclusion of the Delphi, where there is insufficient representation from specific groups. Purposively selected participants will be sent an email per the contact details they have provided at an earlier stage to invite them to participate. Verbal consent will be obtained at the beginning of the session. The number of participants selected to participate in the final virtual consensus meeting is a pragmatic decision based on balancing sufficient representation to incorporate all perspectives with a manageable number of participants that gives everyone a chance to contribute.

Data collection and analysis

The conduct of the virtual consensus meeting will be dependent upon the number of outcomes that need to be discussed based on the results of the Delphi survey. Allowances

will be made for multiple meetings to facilitate international participation across time-zones, and where the number of outcomes to discuss is likely to exceed one to two hours of discussion the meeting may be split into two sessions. The virtual consensus meeting will consist of a voting system as well as open sections of discussion. An overview of the CODECS projects results to date will be presented at the start of the meeting, followed by proposal of each outcome that satisfied the inclusion criteria set out in the Delphi survey. Participants will have the opportunity to discuss each outcome before lodging a vote for its inclusion or exclusion, with outcomes that achieve >75% consensus being included. The core outcome set literature varies in its approach to consensus thresholds for the consensus meeting, with the majority setting a minimum of 70%. A slightly higher threshold of 75% is favoured by some authors as it allows for increased stringency in the final step of the consensus process and we have elected this approach.[21,22] Results will be presented after the voting is complete, outlining which outcomes reach consensus for inclusion in the core outcome set. Those that reach consensus for exclusion or that have no consensus will be reviewed, with panel members having an opportunity to provide an opinion if they see a fundamental reason why they disagree with the exclusion of these outcomes. Should the number of outcomes that reach consensus for inclusion be unwieldy, we may consider a tiered approach for reporting of the core outcome set, as has been done by previous COS developers.[23] Should time allow, we will finish the meeting with a discussion focusing on the definition of outcomes, appropriate outcome measures, and reporting and implementation of the COS; however these will need to be addressed in more detail in subsequent research. The discussion sections of the meeting will be transcribed verbatim and analysed using thematic analysis as described for the focus groups/interviews above.

Dissemination and implementation

This COS will be reported according to the Core Outcome Set-STAndards for Reporting (COS-STAR) reporting guidelines.[24] Efforts for dissemination and implementation will include publishing the COS in an open-access journal, presenting the findings at conferences of relevant professional organisations, sharing with clinical trial registries, and encouraging stakeholder participants to circulate the final COS to their professional networks internationally.

2.4 Discussion

RGCS is one of the most widely available genetic tests internationally and has the potential to provide families with information about their reproductive risks and allow them to make informed decisions in family planning and pregnancy. As with many other types of genetic testing, it is not clear what outcomes are best to assess when considering the impact of RGCS, which has led to marked heterogeneity within the literature and hindered policy-makers in their attempts to utilise high-quality research evidence to support its implementation into routine clinical practice. Contingencies exist from a policy perspective in such cases, allowing expert consensus to be used to make practice recommendations; however this does not address the underlying issues.

This study will provide researchers with guidance on which outcomes to include, at a minimum, in any study evaluating RGCS. As has been seen in other contexts, the application of a COS ensures that a minimum set of outcomes are routinely reported in all studies on a particular topic, allowing reliable comparisons across studies to be achieved. It also facilitates the combining of data where appropriate for use in meta-analyses to quantify outcomes. As the context of RGCS can be diverse, from single gene panels through to expanded panels of hundreds to thousands of conditions, measuring a core set of outcomes across different contexts will allow direct comparison and have the potential to highlight differences that arise when targeted versus expanded screening is offered. Such comparisons may reveal benefits, risk or challenges that may be specific to different contexts and allow for tailored approaches to implementation that address the individual needs of targeted versus expanded offers. Reporting bias is minimised by requiring that the COS is always reported as a minimum, meaning that even non-significant changes will be represented in the literature. Differences that do not reach significance in studies with small sample sizes may reach significance when combined in a meta-analysis. The COS will ensure that outcomes that are relevant to patients are incorporated in future studies. The development of this COS will have implications beyond RGCS, to other forms of genetic testing, and assist in ongoing efforts to define outcomes of genetic services and genetic counselling.

2.5 Amendments to the protocol

Throughout the course of conducting the projects reporting in Chapters 3-6, amendments to the planned protocol were made. The amendments and reasons for these changes are summarised in the table below:

Table 3: Summary of amendments to the published protocol

Study stage	Protocol description	Amendments (with reasons)
Qualitative study	Grounded theory is stated to be utilised in the protocol above.	Upon further conceptualisation of the goals of the qualitative project, reflexive thematic analysis was determined to be a more appropriate method. The theoretical underpinnings for this study are discussed in Chapter 5.
Consensus process	An international consensus process incorporating a Delphi survey and virtual consensus meeting is outlined in the protocol above	The planned international consensus process remains the key final stage of the CODECS study, however, an Australian and New Zealand only Delphi survey was conducted to accommodate the scope of works able to be completed and reported in this thesis. Specific changes to the previously presented protocol are summarised in the supporting information for Chapter 6 (Appendix D)

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Chapter 3: Systematic review of quantitative studies

3.1 Chapter overview

In the following two chapters, I provide a review of the current knowledge about the outcomes of reproductive genetic carrier screening. A sequential systematic review was conducted to review the quantitative literature (presented in Chapter 3), and this is followed by a review and comparison with the qualitative literature (presented in Chapter 4).

This chapter is structured per the corresponding published journal article.

> Richardson E, McEwen A, Newton-John T, Crook A, Jacobs C. Systematic review of outcomes in studies of reproductive genetic carrier screening: Towards development of a core outcome set. *Genet Med*. 2021;24(1):1-14. doi: https://doi.org/10.1016/j.gim.2021.08.005

3.2 Abstract

Purpose: Current practice recommendations support the widespread implementation of reproductive genetic carrier screening (RGCS). These consensus-based recommendations highlight a research gap, with findings from current studies being insufficient to meet the standard required for more rigorous evidence-based recommendations. This systematic review assessed methodological aspects of studies on RGCS to inform the need for a core outcome set.

Methods: We conducted a systematic search to identify peer-reviewed published studies offering population-based RGCS. Study designs, outcomes, and measurement methods were extracted. A narrative synthesis was conducting using an existing outcome taxonomy and criteria used in the evaluation of genetic screening programs as frameworks.

Results: Sixty-five publications were included. We extracted 120 outcomes representing 24 outcome domains. The most frequently reported outcome domains were primary outcomes of RGCS, intention and uptake, need for further testing, pregnancy outcomes, and barriers and facilitators. Of the 24 outcome domains, only 4 included outcomes measured using a patient-reported outcome measure. Heterogeneity in outcome

selection, measurement methods and time points of assessment was extensive. Quality appraisal raised concerns for bias. We found that reported outcomes had limited applicability to criteria used to evaluate genetic screening programs.

Conclusions: Despite a large body of literature, diverse approaches to research have limited the conclusions that can be cumulatively drawn from this body of evidence. Consensus regarding meaningful outcomes for evaluation of RGCS would be valuable first step in working towards evidence-based practice recommendations, supporting the development of a core outcome set.

3.3 Introduction

Population-based reproductive genetic carrier screening (RGCS) identifies individuals and couples with an increased risk of having a child affected by a recessive or X-linked condition.[1] Practice recommendations support the widespread offer of RGCS to the general population, endorsing the discussion of RGCS with all women planning a pregnancy or during their first trimester and promoting informed choice to accept or decline the offer.[2-4] Such practice recommendations are guided by evidence from published research and expert consultation, with a grading system used to indicate the type and quality of evidence available to support each recommendation.[5,6] In the case of RGCS, practice recommendations have utilised expert consensus as the primary source of evidence, indicating that the published literature has been insufficient to inform more rigorous evidence-based recommendations. Considering evidence-based practice as a key goal of medicine, there is a need for integration of clinical expertise with the best available evidence from systematic research.[7] As consensus-based recommendations drive the widespread implementation of RGCS in the general population it is crucial to assess the impacts, benefits and potential harms using rigorous methods. It is timely to consider the issues that exist in the current body of evidence and how these can be addressed to ensure that future studies can reliably inform evidence-based implementation of RGCS.

Previous systematic reviews have examined RGCS programs for specific conditions or focused on areas of particular interest, including reasons for uptake, informed choice, and reproductive decisions.[8-13] These systematic reviews all mentioned difficulty in synthesising data due to heterogeneity in study design, selection of outcomes, or measurement methods. Of particular note, two Cochrane systematic reviews identified no eligible studies due to stringent inclusion criteria requiring randomised or quasi-

randomised study design, which were absent at the time of these reviews.[14,15] We hypothesised that diverse approaches to research as noted in previous reviews may account for the reliance on consensus-based recommendations for RGCS. If this is the case, the development of a core outcome set (COS) may be appropriate.

A COS is a minimum set of outcomes that should be measured and reported in all studies on a particular topic.[16] The development of a COS involves a multi-step consensus process incorporating key stakeholder groups. This systematic review is the first of these steps, and will be followed by a systematic review of qualitative literature, focus groups and interviews with patients, and a consensus process consisting of a Delphi survey and consensus meeting, details of which are outlined in full in the Core Outcome Development for Carrier Screening (CODECS) Study protocol.[17] When implemented into research, a COS ensures that a small number of outcomes are consistently available for comparison across studies, minimises outcome-reporting bias by ensuring that core outcomes are always reported regardless of significance, and maximises the relevance of outcomes due to the input of key stakeholders, including patients. This systematic review aims to assess the methodology used in studies that have implemented RGCS to inform the need for a core outcome set.

3.4 Material and methods

This systematic review was registered with PROSPERO (CRD42019140793) and conducted per the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement and guidance from the Core Outcome Measurement in Effectiveness Trials (COMET) Initiative.[16,18] We searched the Cochrane Database of Systematic Reviews, the Joanna Briggs Institute Systematic Reviews database, MEDLINE, and PROSPERO to ensure that no similar systematic reviews were underway.

3.4.1 Search strategy

MEDLINE, EMBASE, CINAHL, and PsycINFO were searched on 1 December 2020 (illustrative search available in Appendix A). We performed forward and backward searching using reference lists of included publications and forward citation through Google Scholar.

3.4.2 Study selection

All peer-reviewed published studies available in English that offered RGCS for recessive or X-linked conditions to participants through a population screening program were eligible for inclusion. Title and abstract screening, then full-text screening was performed in 10% increments by two independent reviewers (ER and AC) until >85% interrater reliability was achieved, with the remainder reviewed by the primary reviewer (ER) only. Any disagreements were resolved through discussion, and where required, by input from a third reviewer (CJ).

3.4.3 Quality assessment and risk of bias

The primary reviewer (ER) scored the quality of the included studies using the QualSyst tool.[19] "Quality" was defined in terms of the studies' internal validity or the extent to which the design, conduct, and analyses minimised errors and biases. As our aim was to determine all previously published outcomes regardless of study quality, the assessment of bias was not used as grounds for exclusion but rather to give an overall evaluation of study quality within the literature.

We assessed outcome reporting bias according to the Outcome Reporting Bias In Trials (ORBIT) study classification system for missing or incomplete outcome reporting.[20,21] Where available, we obtained published protocols for included studies and compared the outcomes to those reported in subsequent publications. We used discrepancies in outcomes between the protocol and subsequent publications to define a low or high risk of outcome reporting bias.

3.4.4 Data extraction

Due to the large number of studies identified through our search, data extraction was conducted in 5-year increments until outcome saturation was reached. This methodology is suitable for situations where the size of the review would be unmanageable if conducted in full.[16] Outcome saturation was defined as the point at which no new unique outcomes were identified, and this occurred within two 5-year cycles (2010-2015, 2016-2020). This approach ensures that data extraction will continue until all relevant outcomes have been identified and prevent missing relevant outcomes from earlier research. For the purpose of this review, only quantitative data was extracted and analysed.

We extracted all outcomes that have been reported in studies of RGCS. Outcomes, and where supplied, their definition, measurement methods and time point were extracted verbatim using NVivo software.[22] The primary outcome was noted when specified, and basic study characteristics extracted. A coding guide was developed and piloted by ER and AC for 20% of studies to ensure consistency in data extraction for the remainder extracted by ER only. We defined study types within overarching categories of observational or experimental design, with further granularity defined by descriptive or analytic (inferential) statistics, single (cross-sectional) or multiple timepoints (cohort), and prospective or retrospective nature.[23]

3.4.5 Data analysis

We performed two approaches to narrative synthesis.[24] Firstly, a narrative synthesis was conducted to categorise study designs, outcomes and measurement methods. The COMET taxonomy was used as a high-level framework.[25] We elected not to define outcomes as adverse events/effects as there is currently no consensus definition for adverse outcomes in the context of genetic testing. Outcomes were grouped into more granular domains by ER, hereafter referred to as CODECS domains, and mapped to the COMET taxonomy. Definition of the domain and grouping of outcomes were developed iteratively with AC and taken to the study management group (CJ, AM, TNJ) for final review and consensus. Twenty-four CODECS study domains were defined (Appendix A). The number of outcomes with similar definitions or themes within each CODECS domain was used to indicate outcome heterogeneity. We analysed the frequency of outcome reporting at the level of individual outcomes, CODECS domains and COMET taxonomy domains. Measurement methods within each CODECS domain were captured and assessed for validation and piloting as an indication of quality. Meta-analysis was not appropriate for the goals of this review.

Secondly, a narrative synthesis was conducted using criteria defined in a review of RGCS for cystic fibrosis.[26] These criteria were used as a framework to determine whether outcomes reported in eligible studies would be applicable to criteria commonly used to evaluate genetic screening programs and inform evidence-based practice recommendations. Four criteria were defined; participation is voluntary with time allowed for consideration and based on consent, the target group is provided with good quality, comprehensible, and balanced information, there is enough evidence that psychological harm caused by the offer and/or participation is negligible, and there is enough evidence

that social harm caused by the offer and/or participation is negligible. This approach was chosen as there are currently no consensus criteria for the assessment of genetic screening programs, and existing criteria used in other screening contexts have been recognised to have limited applicability for genetic screening programs.[26-28]

3.5 Results

3.5.1 Search strategy

Our literature search identified 2,923 records. After de-duplication and title and abstract screening, 430 publications remained. The remaining publications were separated into 5-year periods, and 230 full-texts published between 2010-2020 were screened. Sixty-five publications from 48 related studies were eligible for inclusion (Figure 4).[29-93]

3.5.2 Study characteristics

Study characteristics are summarised in Table 4. Eligible studies were from 15 countries, with the highest output from the USA (n=14, 29%), Australia (n=6, 13%) and Italy (n=6, 13%). The most frequently reported RGCS programs were for haemoglobinopathies (n=14, 31%), targeted panels in founder populations (n=11, 21%), and expanded carrier screening panels (n=11, 21%).

3.5.3 Quality assessment and risk of bias

Quality scores correlated to more rigorous study designs, with randomised controlled trials (RCTs) scoring highest (mean=0.96, range = 0.92-1.0), followed by analytic studies (mean=0.87, range=0.61-1.0), and descriptive studies (mean=0.79, range=0.43-1.0). These results reflect the expected increase in potential bias that is introduced by less rigorous study designs. Scoring per study is available in Appendix A.

Outcome reporting bias could not be assessed for most studies (n=45, 94%). Three protocols were available: two RCTs[44,94] and an analytic cross-sectional study[95]. The first protocol demonstrated consistency in the measurement, analysis and reporting of all outcomes that were defined in their published protocol.[37,44,45] No missing data were identified, and therefore the ORBIT classification was not applied. The second protocol defined ten outcomes, nine of which were published.[72,95] ORBIT Classification F was applied, indicating a low risk of outcome reporting bias for this study. The third protocol defined 16 outcomes; three of these were represented in publications included in this review, one was reported for a subset of patients only, and one was reported in a publication not included in this review but known to the authors.[41,50,62,94] Six published

outcomes did not correspond to a defined protocol outcome. Eleven outcomes defined in the protocol were not identified in publications to date and constitute missing data from this review. Due to inconsistencies between the protocol and publications, ORBIT classification E was applied, indicating a high risk of outcome reporting bias for this study.

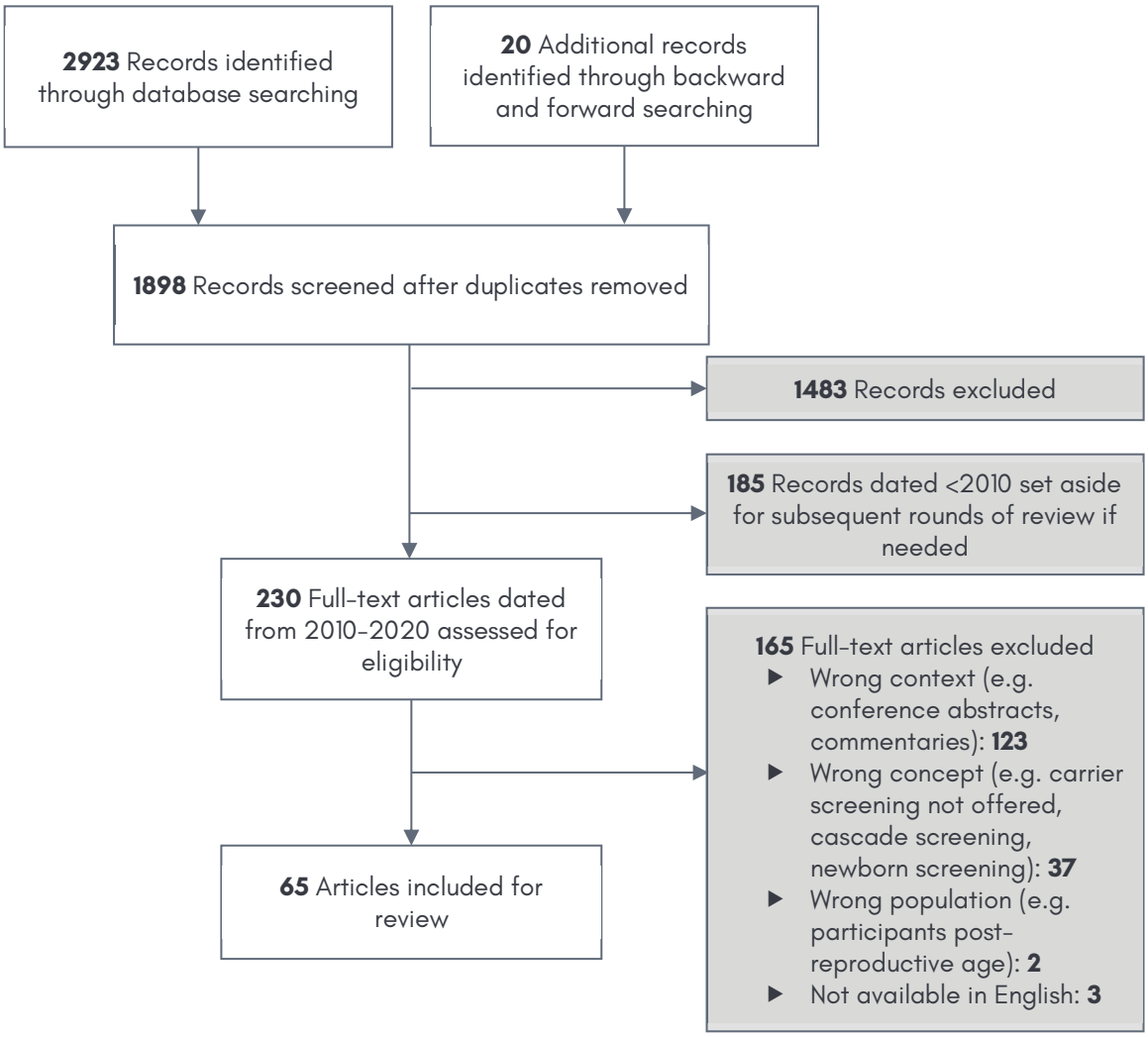

Figure 4: PRISMA diagram for quantitative studies

3.5.4 Study designs

Most studies were observational in design (n=46, 96%), with only two RCTs identified. A protocol for a third RCT was identified; however, no publications were available. Most studies provided descriptive statistics (n=35, 73%), collected cross-sectional data (n=42, 88%), and were retrospective in nature (n=30, 63%). The most common study type was descriptive cross-sectional studies, representing audit-style summaries of a screening offer (n=33, 69%). A detailed summary of included studies can be found in Appendix A.

Table 4: Characteristics of included studies

Descriptor	Number of Studies
Study design (N=50)[a,b]	
Observational (n=48)	
Analytic Cohort, Prospective	1
Analytic Cohort, Retrospective	3
Analytic Cross-Sectional, Retrospective	9
Descriptive Cohort, Prospective	2
Descriptive Cross-Sectional, Prospective	14
Descriptive Cross-Sectional, Retrospective	19
Experimental (n=2)	
Randomised Controlled Trial	2
Year of publication (N=65)	
2020-2016	33
2010-2015	32
Country of study (N=48)[a]	
Australia	6
China	2
Greece	2
India	2
Israel	3
Italy	6
Korea	1
Lebanon	1
Taiwan	2
Thailand	2
The Netherlands	3
Turkey	2
UAE	1
UK	1
USA	14
Population[b]	
Individuals undertaking RGCS	
Prenatal only	11
Preconception only [c]	6
Either	31
Increased risk couples identified through RGCS	2
Intervention[b]	
Haemoglobinopathies	16
Targeted panel in founder population	11
Expanded carrier screening (ECS)	11
Cystic fibrosis (CF)	4
Fragile X (FXS)	3
Spinal Muscular Atrophy (SMA)	4
3-gene panel (CF, FXS, SMA)	3

[a] 65 publications from 48 studies

[b] Some related studies included multiple study designs, populations, or interventions depending on sub-analyses published independently

[c] Includes compulsory pre-marital screening programs

3.5.5 Frequency of study outcomes

One hundred and twenty outcomes were extracted (full list available in Appendix A). The average number of outcomes reported per publication was seven (range 1-23). Only 8% (n=5) of publications defined the primary outcome(s). The most frequently reported outcomes across studies were detection rate based on either DNA analysis or biochemical assays (n=39, 81%), identification of increased risk couples (n=26, 54%), uptake of prenatal diagnosis (n=22, 46%), and results of prenatal diagnosis (n=20, 42%). Outside of clinical outcomes directly related to test results or pregnancy outcomes, the most frequently reported outcomes were uptake of RGCS (n=17, 35%), knowledge pertaining to the test offer (n=10, 21%), and anxiety (n=8, 17%).

3.5.6 Outcome domains and heterogeneity

Outcomes were grouped into 24 CODECS domains, with a range of 1-11 outcomes per domain, with higher numbers being indicative of outcome heterogeneity. CODECS domains were mapped to the COMET taxonomy (Figure 5), with the highest proportion of outcomes in the domain of 'delivery of care' (n=48, 40%).

The frequency of reporting per CODECS domain is shown in Figure 6. The most frequently reported CODECS outcome domains were ‘primary outcomes of RGCS’ (n=39, 81%), ‘intention and uptake’ (n=34, 71%), ‘need for further testing’ (n=29, 60%), and ‘pregnancy outcomes’ (n=21, 44%). Of the domains that included patient-reported outcomes, 'knowledge’ was the most frequently reported. Most outcome domains demonstrated outcome heterogeneity. Two were most notable due to the degree of heterogeneity and the fact that they were frequently reported in studies on RGCS; psychological wellbeing and timeliness.

The outcome domain of 'psychological wellbeing' was reported in 20% of studies.[43,44,54,56,62,71,72,76,89,92] Ten different outcomes were used to measure psychological wellbeing; anxiety, concern, depression, feelings about results, perceived ability to cope, predicted negative feelings, reassurance, stress, subjective distress, and worry. Of these, the most frequently reported was anxiety. Most studies measured more than one psychological outcome (range: 1-3). Use of validated measures and timepoints of assessment were highly variable.

The outcome domain of 'timeliness' was reported in 20% of studies.[33,44,45,49,60,68,71,73,86,93] We defined timeliness as the provision of RGCS and follow-up testing, typically in the prenatal setting, in a manner that allowed sufficient time for

deliberation and decision-making. Eleven different outcomes were reported pertaining to timeliness; gestational age when offered RGCS, gestational age at uptake, the time between pregnancy confirmation and RGCS, turnaround time for results, time between maternal results and partner testing, gestational age at the time of partner results, gestational age at the time of prenatal diagnosis, proportion screened by 10-, 12-, 16- and 26-weeks' gestation. There was a lack of consistency in defining gestations by which services were considered to have been delivered in a timely manner. Reporting was variable, with mean, median and range being used interchangeably.

3.5.7 Measurement methods

Various measurement methods were extracted from eligible studies, with most outcomes measured using an investigator-derived scale (n=66, 55%) or extracted from clinical or laboratory databases (n=52, 43%). Only a minority of outcomes (n=14, 12%) were measured using a previously reported or validated patient-reported outcome measure, all of which were in the domains of psychological wellbeing, knowledge, decision satisfaction/regret and deliberation/informed choice (Appendix A).

Twelve publications from 10 studies assessed knowledge, each using a different measurement method. One used a validated knowledge scale that was designed specifically for their study[72], four adapted a previously published scale that had been validated for use in a different context[37,44,54,55,80], three adapted a previously published scale that had not undergone formal validation[53,71,89], one developed a new scale and piloted it before use[39], and one provided insufficient information regarding the measurement method[48]. Where a previously published scale was adapted, the integrity of the validation or piloting of the original scale was often compromised by the addition or removal of questions, changes in wording, or merging of multiple previous scales into a new scale. Only one study performed formal validation of the adapted scale[37,44], one study piloted the adapted scale[71], and five studies did not report any piloting or validation of the adapted scale[53-56,80,89].

Time points of measurement were also variable. A single time point was assessed by most studies (n=41, 85%) and included audit data from databases between 1-30 years since screening (n=34, 83%)[29,30,32-36,38,40,42,47-49,52,57,60,61,63-65,67-69,73,74,78,81,83-88,90,91,93], patient-reported outcomes at pre-test counselling after the decision to accept or decline was made (n=3, 7%)[75,76,82], after maternal results but before partner results (n=1, 2%)[39], and after results between 1-2 years since screening (n=3, 7%)[46,51,53,55,56,58,59,66,92]. Seven studies

(15%) measured outcomes at multiple time points including before attending pre-test counselling (n=2, 4%)[79,80], before and after education (n=1, 2%)[89], at pre-test counselling when decision to accept or decline was made (n=5, 12%)[37,41,43-45,50,54,62,70-72], and after results ranging from 2 weeks to >10 years after screening (n=6, 15%)[37,41,43-45,50,54,62,70-72,77,79,80].

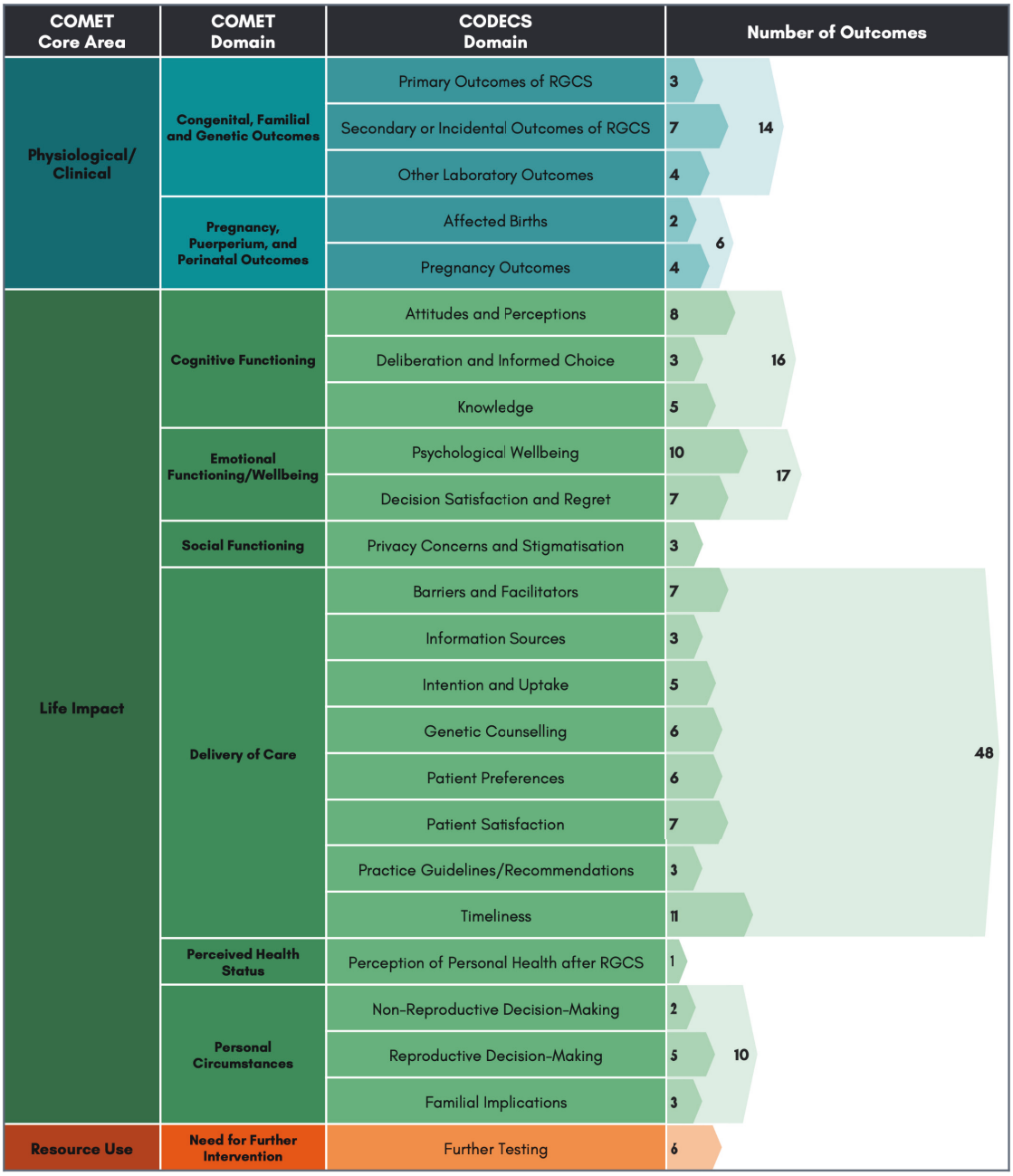

Figure 5: Summary of outcomes per domain
Mapped to applicable core area and domains from the COMET taxonomy.

3.5.8 Criteria for assessment of genetic screening programs[26]

Participation is voluntary with time allowed for consideration and based on consent

CODECS outcome domains of 'intention and uptake', 'attitudes and perception', 'decision satisfaction and regret', and 'deliberation and informed choice', were mapped to the above criterion. Intended or actual uptake was reported in 71% (n=34) of studies[30,32-38,40-42,44,48-53,55-57,60,61,63,65,69-72,74,75,77-80,84-87,89,93]. The outcome domain of 'attitudes and perceptions', which includes outcomes that assess how attitudes or perceptions influence test uptake, was reported in 23% (n=11) studies[37,44,54,55,62,71,72,76,80,82,89,90,92]. Outcome domains of 'decisional satisfaction and regret' and 'deliberation and informed choice' were reported by 15% (n=7)[43,44,54,55,62,71,75,92] and 6% (n=3)[37,44,72,79,80] of studies respectively.

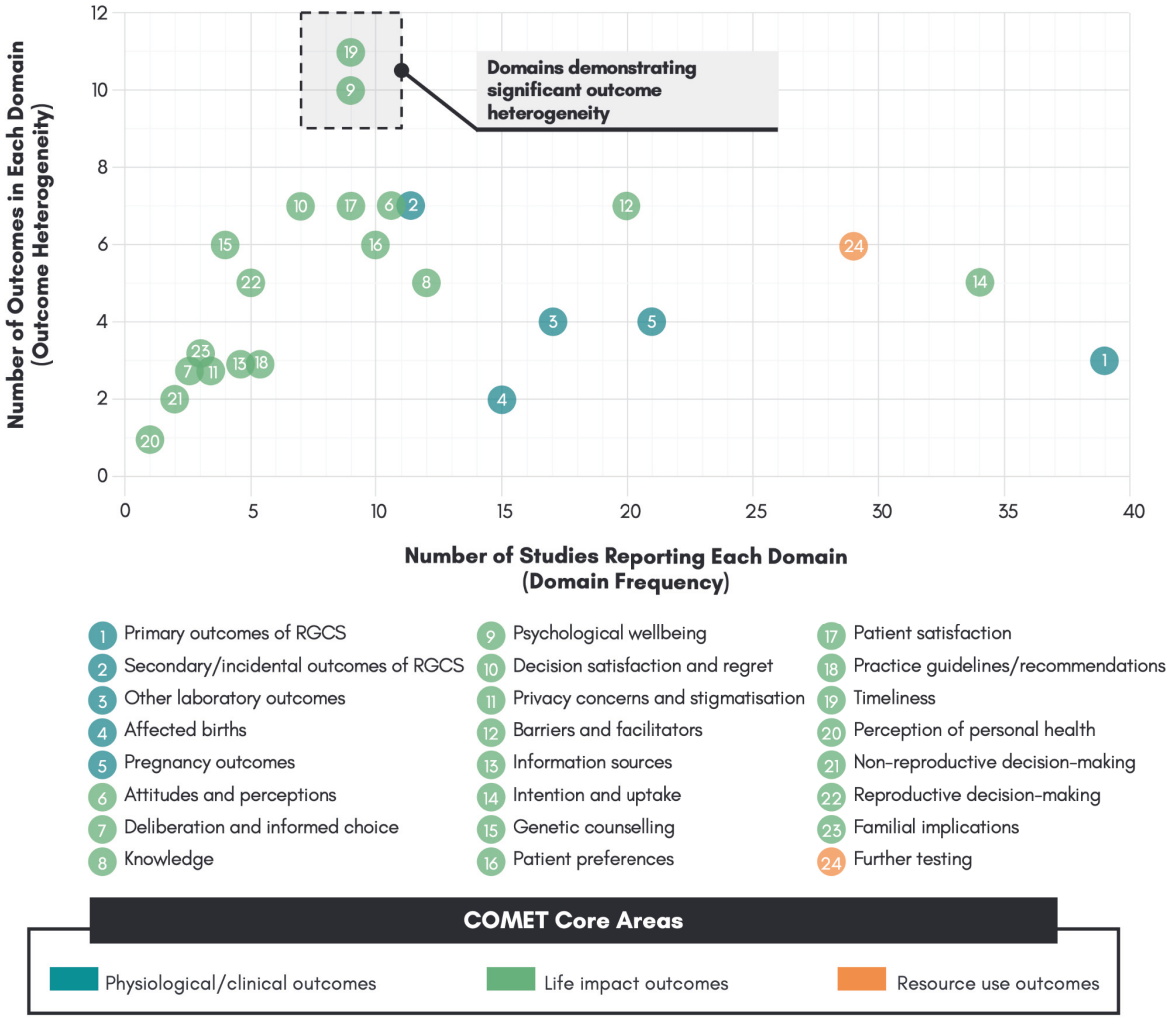

Figure 6: Domain frequency and outcome heterogeneity

Visualising outcome heterogeneity in conjunction with frequency of domain reporting highlights domains that are most problematic when considering consistency and comparability in the research literature. COMET core areas indicated by colour, CODECS Outcome Domains numbered 1-24.

The target group is provided with good quality, comprehensible, and balanced information

CODECS outcome domains of 'knowledge' and 'patient satisfaction' were mapped to this criterion. Knowledge was the most frequently reported of these outcome domains, with 25% (n=12)[37,39,42-44,48,53-56,71,72,75,80,89] of studies assessing outcomes such as knowledge of the screening offer, recall, and understanding. Patient satisfaction was reported in 15% (n=7) of studies, assessing outcomes such as helpfulness of educational materials, feeling information needs were met, and satisfaction with pre-test genetic counselling.

There is enough evidence that psychological harm caused by the offer and/or participation is negligible

CODECS outcome domains of 'psychological wellbeing' and 'perception of personal health status after RGCS' were mapped to this criterion. Psychological wellbeing was reported in 20% (n=9) of studies[43,44,54,56,62,71,72,76,89,92], and perceptions of personal health status was reported in a single study[71].

There is enough evidence that social harm caused by the offer and/or participation is negligible

CODECS outcome domains of 'affected births', 'reproductive decision-making', 'non-reproductive decision-making', 'familial implications', and 'privacy concerns and stigmatisation' were mapped to this criterion. The outcome domain of 'affected births' was reported in 31% (n=15) of studies[29,30,32,35,38,40,48,58,60,64,67,69,73,84,86]. The outcome domain of 'reproductive decision-making' was reported in 10% (n=5) studies[46,58,59,62,70,71,76,92]. Assessment of social impact or harms outside of reproductive decisions and birth rates was limited to a handful of studies and included assessing the impact of results on the couple's relationship, dissemination of results to family members, concerns regarding discrimination by insurance companies, and fear of stigmatisation within the community[52,54,62,71,89].

Box 1: Significance of systematic review findings

Summary of findings:

- 24 outcome domains were identified that capture the research landscape evaluating RGCS to date
- Selection of outcomes and measurement methods were heterogenous
- Indications of bias in the current literature were identified
- Cross-sectional and audit-style papers were over-represented
- Descriptive statistics were prevalent, limiting causal inferences or associations
- Patient perspective was lacking, with few studies including patient reported outcomes and no reported involvement of patients in study design
- Studies rarely defined primary outcome(s), highlighting a lack of consensus for how to assess clinical utility of RGCS
- Outcomes had limited applicability to criteria used to evaluate genetic screening programs
- Potential harms of RGCS, including psychological or social harms, cannot be robustly concluded from the current literature.

How can a core outcome set help?

- Heterogeneity of outcomes and measurement methods will be minimised by defining a small number of outcomes that are recommended for all future studies.
- Involvement of key stakeholders in the identification and definition of core outcomes maximises relevance of research findings, with patients and policy-makers principally of concern from this review.
- Defining primary outcome(s) of RGCS will provide clarity in future studies aiming to evaluate RGCS offers.

3.6 Discussion

A lack of consensus for 'what to measure' in research evaluating health interventions is a major challenge across the medical field and has been recognised to limit reliability of the conclusions that can be drawn from research evidence.[96] Significant inconsistency in the choice of outcomes, measurement methods, and a lack of outcomes informed by patients as end-users have been noted across medical specialities, including in reviews on clinical genetic service outcomes.[97,98] Increasingly, discussions within the genetics community focus on how we can best define healthcare outcomes to capture the value of genetic services, genetic counselling, and genetic testing.[99,100] This review is the first step in a structured approach to addressing this question.

Across studies of population-based RGCS, we identified potential biases introduced by study design, heterogeneity in outcome selection, and variability in measurement methods. We found that outcomes had limited applicability to criteria used to evaluate genetic screening programs. While consensus-based practice recommendations have led to increasing support for the widespread offer of RGCS to the

general population, in order to achieve the goal of evidence-based medicine, it is imperative to address the issues highlighted in this review to generate research that can inform evidence-based practice recommendations as we move forward.[7]

We found that study designs compromised the quality of evidence from the current literature. Firstly, there were a large number of observational studies that have the potential to introduce biases at the stage of design and conduct, with selection and measurement biases principle amongst these. We also found a high risk of outcome reporting bias in one of only two randomised controlled trials on this topic. Secondly, previous reviews have recognised the prevalence of cross-sectional studies as a methodological limitation of research on genetic testing and counselling.[100] Our findings are consistent with these reviews, with a predominance of cross-sectional studies and limited follow-up of outcomes over time, reiterating the necessity for longitudinal approaches to future research. Thirdly, a previous review has highlighted that a lack of analytic statistics impeded efforts to infer factors influencing decision-making and their relative contributions.[10] Our findings similarly revealed favouring of descriptive, as opposed to analytic, statistics that may limit the conclusions that can be drawn from data. Finally, we observed an oversaturation of audit-style studies drawing from clinical and laboratory databases. Whilst representing widespread international efforts to implement RGCS, these studies failed to contribute new findings and lacked patient-reported outcomes. As patient-centeredness is a core tenet of genetic counselling and medical practice, and it is well recognised that patient-reported data enriches information about relevant outcomes that reflect their experiences, we found the lack of patient voice in data collection concerning.[101-103] We identified a small number of well-designed studies that addressed biases, measured outcomes longitudinally, performed analytic statistics, and incorporated patient-reported outcomes; however, further work is needed to expand on the body of evidence they have created. Whilst randomised controlled trials are considered the gold-standard for generating unbiased research evidence, they are resource-intensive and may not be suitable for this context. Instead, efforts must be taken to ensure that future research on RGCS has clearly defined research questions that inform the study design, and that potential biases are addressed and minimised.

Capturing all reported outcomes from studies on RGCS provided insights into research priorities over the past decade. We identified an emphasis on delivery of care; focusing largely on barriers and facilitators to uptake, patient preferences, and

satisfaction. This focus is not surprising considering that the context of RGCS has largely been in either increased risk populations with a public health imperative to reduce disease incidence, or broadly through commercial initiatives with a financial interest in uptake. Therefore, measuring uptake has been widely used to illustrate the acceptability of RGCS and provide a rationale for its continued offer. The skewing towards operational outcomes such as uptake however, results in a lack of insight into the patient experience and limits understanding of the benefits and harms of testing. It is evident that the relevance of outcomes being assessed needs further consideration and could benefit from the inclusion of patients at the inception of research design. Funding bodies are increasingly placing emphasis on consumer and community engagement, and systematic reviews have highlighted the positive impact that patient and public involvement can have on research quality, appropriateness and relevance.[104,105] Previous core outcome sets involving patients in the design and conduct of research led to the identification of outcomes that were not defined by health professionals or researchers alone.[16] We did not find any evidence of patient involvement in the design of research or selection of outcomes in this review. The absence of patient involvement at the outset of study design and under-representation of patient-reported outcomes in the RGCS literature emphasises the need for a clearer patient voice in future research.

Demonstrating the clinical utility of a health intervention is a central aim of research, however this review found that clinical utility has not been clearly illustrated for RGCS. When considering the goals of RGCS, two perspectives on clinical utility are apparent; a reduction in disease incidence, or the provision of information to allow reproductive autonomy and informed decision-making. Whilst most studies in this review did not define a primary outcome, reduction in disease incidence was frequently inferred as a primary outcome. This is problematic from an ethical perspective, as a focus on reducing incidence may be perceived as under-valuing the lives of those currently living with genetic conditions.[106] It is increasingly evident that the clinical utility of RGCS is more appropriately reflected by the latter perspective that strives to enhance reproductive autonomy and informed decision-making. Furthermore, an important element of clinical utility is timing, as the usefulness of information provided by RGCS is contingent upon whether patients have sufficient time to consider their options, are not precluded from options due to advanced gestation, and are not being put at risk for regret or poor psychological outcomes insofar as is possible in a prenatal setting. Most studies did not report any aspect of timeliness, and in those that did, we found a lack of consensus for

how to do so. Previous systematic reviews have highlighted that despite RGCS being ideally conducted preconceptionally, testing during pregnancy remains prevalent.[11,12] Even as awareness of RGCS increases, many people may not appreciate its importance or be motivated to pursue it until they are pregnant, may have unexpected pregnancies, or be subject to health disparities that limit access. As long as RGCS continues to be offered in a prenatal setting, providing clarity around outcomes that account for timing will be crucial to evaluate screening programs and appropriately capture clinical utility for patients.

Evidence-based practice recommendations provide crucial guidance to practitioners regarding the safe and effective implementation of health interventions. We identified significant gaps in the body of evidence used to inform practice recommendations, which likely accounts for the reliance on consensus-based recommendations to date. The informed and voluntary nature of decision-making was compromised by a focus on uptake, which is an insufficient proxy for informed choice. A previous systematic review highlighted that many people accept screening simply because it is offered and not due to perceived benefits.[26] More informative measures of deliberation, informed choice, and decisional satisfaction/regret were identified in this review, albeit less frequently, and should be a focus of future research to ensure that data representative of informed and voluntary screening is available for evaluation. Studies rarely assessed the quality of pre-test information and counselling. Some studies assessed patient satisfaction, which can be a valuable indicator of the quality of genetic counselling and information provision. Notably, despite validated satisfaction scales for genetic counselling being available, these were not utilised in any studies.[107] Ensuring that patients receive appropriate pre-test counselling will become more important as a diverse range of health professionals become involved in offering RGCS and as testing is scaled to encompass the general population. It is imperative to ensure that appropriate standards of knowledge are being fostered to meet evaluation criteria that strive towards informed decision-making.

Evaluation criteria also aim to understand the potential adverse outcomes of a health intervention in order to minimise harm to patients. In the context of RGCS, perceived risks include impacts on psychological wellbeing and possible social consequences, such as discrimination or stigmatisation. Previous reviews have indicated that psychological distress may occur at various stages of the screening process but is often not sustained.[12,108] However, the heterogeneity observed in the outcomes used to

assess psychological wellbeing in this review, coupled with the variability in measurement methods and time points, detracts from how confidently we can draw conclusions about potential psychological harms. The impact of potential biases that we found in this review may also have flow-on implications for measuring psychological outcomes, including selective reporting biases which may skew published evidence towards favourable outcomes and selection bias which may limit generalisability of findings to the wider population. Many RGCS programs incur an out-of-pocket cost to participants and favour higher socioeconomic groups; as RGCS becomes accessible to the general population, it is crucial to establish the external validity of existing findings by evaluating psychological outcomes in more diverse populations.[100] Deciding on which outcome(s) best capture psychological wellbeing, minimising selection bias, and ensuring transparent reporting of all outcomes regardless of the results, will be necessary to provide greater certainty that RGCS results in negligible psychological harms. In regard to social consequences, little has been done to address these. We identified a small number of studies that considered impact of results on relationships and potential for stigmatisation or discrimination, however further work is needed to more fully understand the social consequences of RGCS.

At an overarching level, heterogeneity in a research dataset limits direct comparisons between studies on the same topic and indicates a lack of agreement for which outcomes can meaningfully represent the impact of an intervention. Where heterogeneity occurs, the ability to capture benefits and harms is compromised.[16,96] Future directions for research will involve clarifying what outcomes are valued by all key stakeholders in RGCS, including consumers, health professionals, researchers and policy-makers. Such research will need to address numerous issues highlighted in this review, starting with what outcomes should be measured, followed by how and when. Further exploration of outcomes related to limitations of RGCS, including patient understanding of residual risks, practical aspects of RGCS, such as ensuring appropriate storage and accessibility of results over time, and methodological aspects of research, including development of validated measurement tools, are areas of interest for future research. Researchers should strive to minimise bias in the design, conduct and reporting of their findings and consider making available a transparent protocol for their research that allows the methods to be clear and reproducible. Evaluation criteria used to assess genetic screening programs should be considered when designing research questions for

future studies to ensure that findings are informative and work towards the goal of evidence-based practice recommendations.

3.7 Limitations

Publications not available in English were excluded due to a lack of resources for translation; nevertheless, we achieved representation from 15 countries. The iterative, inductive process used to extract outcomes and group them into domains may introduce biases from the reviewer; however, we minimised this by applying two independent reviewers and evaluating final domains and outcome groupings with the study management group. This review includes only quantitative data from the RGCS literature. More patient-centred outcomes will likely be evident in the qualitative literature, planned as a subsequent review by these authors.

3.8 Conclusion

Lack of consensus regarding outcomes to measure in the evaluation of RGCS perpetuates our inability to definitively demonstrate the impact, benefits and harms of RGCS at the standards required for evidence-based practice recommendations. Consensus on how to approach future research on this topic, including consideration of appropriate study designs that reduce bias, enrich understanding through the capture of longitudinal outcomes, and incorporate relevant outcomes informed by patients and other stakeholders, is needed. This review provides a strong rationale for the development of a core outcome set for RGCS.[17]

3.9 Summary of supporting data available in Appendix A

The following supporting data are available in Appendix A:

Supplementary material A.1 – Illustrative search strategy

Supplementary material A.2 – COMET/CODECS taxonomy version 1.0

Supplementary material A.3 – Summary of included studies

Supplementary material A.4 – Risk of bias assessment

Supplementary material A.5 – List of outcomes extracted from quantitative studies

Supplementary material A.6 – Block diagram of outcomes reported per study

Supplementary material A.7 – Outcome measurement methods

3.10 References

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Chapter 4: Systematic review of qualitative studies

4.1 Chapter overview

In this chapter, I present the sequential systematic review of qualitative studies and a comparison of the qualitative findings with those from the quantitative literature described in Chapter 3.

This chapter is structured per the corresponding published journal article.

> Richardson E, McEwen A, Newton-John T, Crook A, Jacobs C. Incorporating patient perspectives in the development of a core outcome set for reproductive genetic carrier screening: A sequential systematic review. *Eur J Hum Genet*. Mar 28 2022;30(7):756-765. doi: https://doi.org/10.1038/s41431-022-01090-1

4.2 Abstract

There is currently no consensus on the key outcomes of reproductive genetic carrier screening (RGCS). This has led to a large amount of variability in approaches to research, limiting direct comparison and synthesis of findings. In a recently published systematic review of quantitative studies on RGCS, we found that few studies incorporated patient-reported outcomes. In response to this gap, we conducted a sequential systematic review of qualitative studies to identify outcomes exploring the patient experience of RGCS. In conjunction with the review of quantitative studies, these outcomes will be used to inform the development of a core outcome set. Text excerpts relevant to outcomes, including quotes and themes, were extracted verbatim and deductively coded as outcomes. We conducted a narrative synthesis to group outcomes within domains previously defined in our review of quantitative studies, and identify any new domains that were unique to qualitative studies. Seventy-eight outcomes were derived from qualitative studies and grouped into 19 outcome domains. Three new outcome domains were identified; 'goals of pre- and post-test genetic counselling', 'acceptability of further testing and alternative reproductive options', and 'perceived utility of RGCS'. The identification of outcome domains that were not identified in quantitative studies indicates that outcomes reflecting the patient perspective may be under-represented in the quantitative literature on this topic. Further work should focus on ensuring that outcomes reflect the real world

needs and concerns of patients in order to maximise translation of research findings into clinical practice.

Keywords: reproductive genetic carrier screening; core outcome set; qualitative systematic review; genetic counselling

4.3 Introduction

Reproductive genetic carrier screening (RGCS) identifies individuals and couples with an increased risk of having a child affected by a recessive or X-linked condition, providing them with information to make informed reproductive choices. Research evaluating RGCS to date has spanned numerous countries with a variety of screening approaches, each working within different healthcare systems and societal settings. RGCS has quickly evolved from a targeted screening approach aimed at individuals with an increased a priori risk, to a widely available, pan-ethnic screening approach offered broadly to the general population. Such rapid advancements in an emerging field have in many instances outpaced research efforts aiming to evaluate the impact, benefits and harms of RGCS. Varied approaches to evaluating RGCS and a lack of consensus regarding the measurable outcomes of RGCS has resulted in heterogeneity across studies. As a result, it has been difficult to utilise existing research literature to inform evidence-based practice recommendations, which are considered the most rigorous approach to guiding clinical practice. Current practice recommendations supporting the offer of RGCS have instead relied on a consensus-based approach.[1-3] The Core Outcome Development for Carrier Screening (CODECS) Study aims to address this issue by developing a set of agreed outcomes in collaboration with key stakeholders including patients, health professionals, researchers and policy-makers; known as a core outcome set (COS).[4] A COS is a minimum set of outcomes that should be measured and reported in all studies on a particular topic and can improve the overall quality, comparability and synthesis of research findings in a body of literature. While there are valuable insights to be gained from existing research efforts in this area, addressing the heterogeneity in research outcomes by developing a COS will ensure that a core set of evidence-based data will be available for future practice guidelines to draw upon.

The initial stage in the development of a COS involves a review of outcomes used in previous studies. The identified outcomes form a baseline 'long list' that is refined during a consensus process involving key stakeholders. A sequential systematic review of

outcomes measured in studies on RGCS was conducted as the first step in the CODECS study. We divided this review according to the data types that were reported, in order to account for the different methodological approaches needed to extract outcomes from quantitative versus qualitative data. This article reports on the findings of the systematic review of outcomes in qualitative studies of RGCS, and compares these with our previously published systematic review of quantitative studies.[5]

This review of qualitative studies contributes to the goal of applying a patient-centred approach to the development of a COS.[6,7] Valuable insight can be derived from involving patients in the COS development process, and has been shown to enhance the relevance of the COS to patients as the end-users and lead to identification of outcomes that were not identified by professional groups alone.[8,9] A key finding from our systematic review of quantitative studies was limited patient-reported outcome measures, and limited evidence of patient and public involvement in the design and conduct of included studies. As a result, the outcomes identified from quantitative literature predominantly reflect the priorities and perspectives of researchers and clinicians. Qualitative research methods provide rich insights into the patient perspective, and where an existing body of published qualitative literature is available, as is the case with RGCS, a systematic review of qualitative studies can be a valuable addition to the COS development process.[10]

Therefore, this systematic review aims (i) to identify outcomes of importance to patients accessing population-based RGCS to consider for inclusion in a COS, and (ii) to compare the outcomes identified from the qualitative literature with those identified in our previous systematic review of outcomes in quantitative studies.[5]

4.4 Material and methods

This systematic review was registered with PROSPERO (CRD42019140793) and conducted per the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement and guidance from the Core Outcome Measurement in Effectiveness Trials (COMET) Initiative.[6,11] We searched the Cochrane Database of Systematic Reviews, the Joanna Briggs Institute Systematic Reviews database, MEDLINE, and PROSPERO and found no similar systematic reviews undertaken or underway.

4.4.1 Search strategy

This review utilised the same search strategy as a previously published systematic review of quantitative studies.[5] MEDLINE, EMBASE, CINAHL, and PsycINFO were searched on 1 July

2021 (illustrative search available in Appendix B). Forward and backward searching was performed using reference lists of included publications and forward citation through Google Scholar.

4.4.2 Study selection

All peer-reviewed published studies available in English that conducted qualitative research with individuals or couples who had accessed population-based RGCS for recessive or X-linked conditions were eligible for inclusion. For the purpose of this review, qualitative methods were defined as interviews or focus groups, and excluded interpretation of open-text responses from surveys. Studies exploring the perspectives of individuals with lived experience of conditions included in RGCS were excluded as the focus of this review was to identify process-specific outcomes from those undertaking RGCS. Title and abstract screening, then full-text screening was performed in 10% increments by two independent reviewers (ER and AC) until >85% interrater reliability was achieved, with the remainder reviewed by the primary reviewer (ER) only. Any disagreements were resolved through discussion, and where required, by input from a third reviewer (CJ).

4.4.3 Quality assessment and risk of bias

Two reviewers (ER and CJ) scored the quality of studies included in both reviews using the QualSyst tool.[12] "Quality" was defined in terms of the studies' internal validity or the extent to which the design, conduct, and analyses minimised errors and biases. Assessment of bias was not used as grounds for exclusion but rather to give an overall summary of quality.

4.4.4 Data extraction

Due to the large number of studies identified through our search, data extraction was conducted in 5-year increments until outcome saturation was reached. This methodology is suitable for situations where the size of the review would be unmanageable if conducted in full.[6] Outcome saturation was defined as the point at which no new unique outcomes were identified, and this occurred within two 5-year cycles (2010-2015, 2016-2020). This approach ensures that data extraction will continue until all relevant outcomes have been identified and prevent missing relevant outcomes from earlier research.

In the systematic review of qualitative studies, no studies were anticipated to have addressed outcomes specifically, as such our approach to data extraction was deductive and guided by methodology outlined in a previous systematic review.[9] Text excerpts relevant to outcomes, including quotes and themes developed by authors, were extracted verbatim using NVivo software.[13] A coding guideline was developed by the primary reviewer (ER) and piloted on 20% of studies with a second reviewer (CJ), and subsequently refined. The primary reviewer conducted the remainder of the data extraction and this was checked for agreement by a second and third reviewer (AC and CJ).

In the systematic review of quantitative studies, used as a comparison herein, we extracted all outcomes, and where supplied, their definition, measurement methods and time point using NVivo software.[13] A coding guide was developed and piloted by two reviewers (ER and AC) for 20% of studies to ensure consistency, with the remainder extracted by the primary reviewer (ER). The primary outcome was noted when specified, and basic study characteristics including study aim and demographics of participants were extracted in both reviews.

4.4.5 Data analysis

Both quantitative and qualitative reviews utilised the same analysis method in order to permit direct comparison of the findings between both reviews. A narrative synthesis was conducted, utilising content analysis to facilitate frequency counts and tabulation of outcome domains represented in the qualitative literature.

The COMET taxonomy was used as a high-level framework to group outcomes, with the hierarchy consisting of 'COMET core areas' followed by 'COMET outcome domains'.[14] We elected not to define outcomes as adverse events/effects as there is currently no consensus definition for adverse outcomes in the context of genetic testing. Outcomes were grouped into more granular domains by ER, hereafter referred to as CODECS domains, and mapped to the COMET taxonomy. Definition of the domain and grouping of outcomes were developed iteratively with AC and taken to the study management group (CJ, AM, TNJ) for final review and consensus. Three new CODECS study domains were defined in addition to 24 domains previously defined in the quantitative review. Minor changes were made to the titles of five existing CODECS domains from the quantitative review to appropriately distinguish them from, or evolve

them in line with new domains identified in the qualitative review, and two similar domains were pooled (Appendix B).

The number of studies reporting each outcome domain were compared between quantitative and qualitative studies to highlight areas of difference. We defined three categories (i) outcome domains that were seen only in qualitative studies (ii) outcomes domains that were seen in both qualitative and quantitative studies (iii) outcome domains that were seen only in quantitative studies. Absolute difference in proportion of studies reporting outcome domains is reported.

4.5 Results

4.5.1 Search strategy

Our literature search identified 2,923 records. After de-duplication and title and abstract screening, 430 publications remained. The remaining publications were separated into 5-year periods, and 230 full-texts published between 2010-2020 were screened. Sixteen publications from 13 studies were eligible for inclusion in this review (Figure 7).[15-30] Six publications were from three mixed methods studies that were also included in our previous systematic review of quantitative studies.[16,18,24,25,27,30]

4.5.2 Study characteristics

Study characteristics are summarised in Table 5 Eligible studies were from six countries, and incorporated a range of screening offers including targeted panels in founder populations (n=5), haemoglobinopathies (n=3), expanded carrier screening (n=3), 3-gene panel (CF, FXS, SMA) (n=2), and single gene screening (n=2). A detailed summary of included studies can be found in Appendix B.

4.5.3 Quality assessment and risk of bias

The mean quality assessment score was 0.67, with a range of 0.45-0.85 (maximum attainable score is 1) indicating a broad range of variability in the quality and risk of bias introduced across these qualitative studies. Of particular note, no studies incorporated reflexivity in the reporting of potential influences of the researcher or study methods on the findings. Few studies provided a description or justification of the theoretical framework or wider body of knowledge informing the study design and methods used. Scoring per study is available in Appendix B.

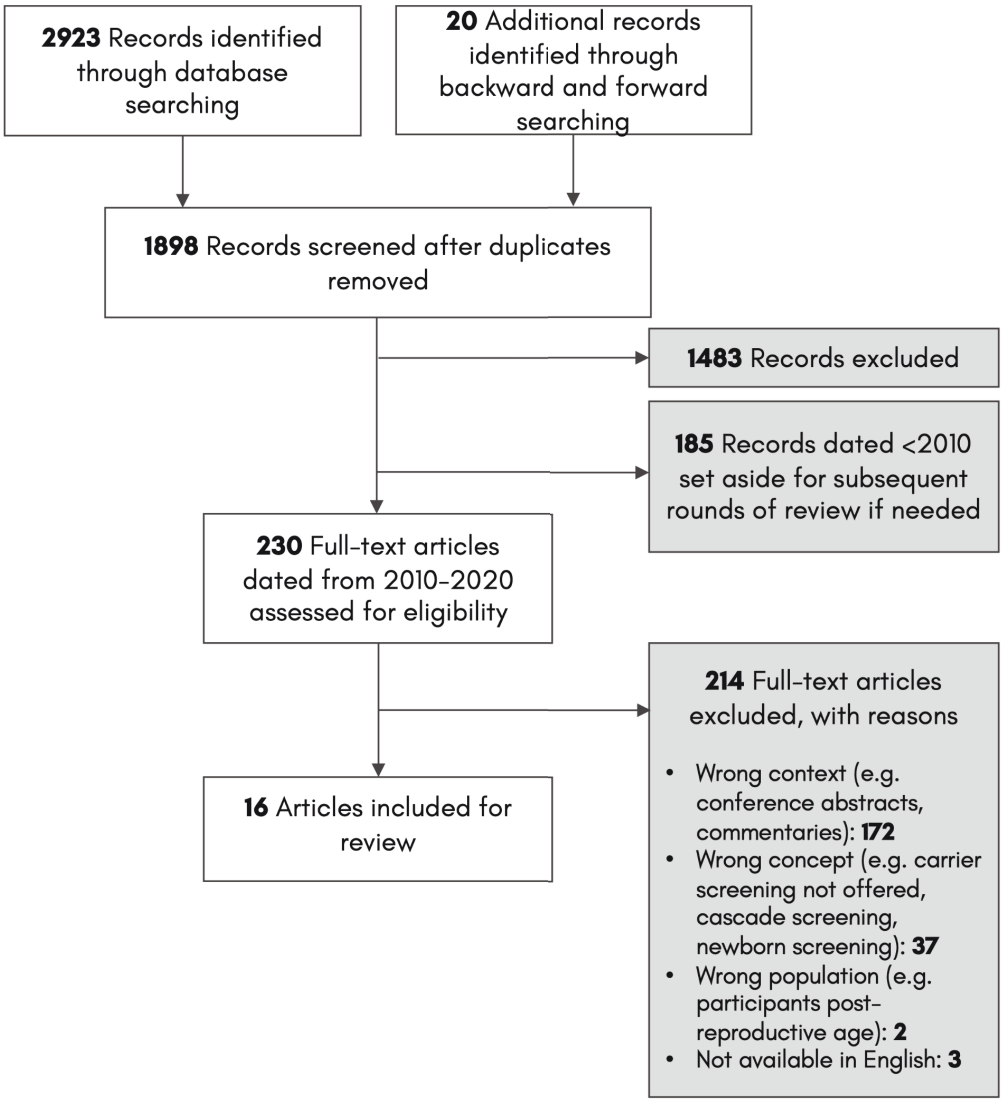

Figure 7: PRISMA diagram for qualitative studies

4.5.4 Outcomes identified in qualitative studies of RGCS

The following results refer to the findings of the qualitative review only.

Overview

Seventy-eight outcomes were derived from qualitative studies included in this review (full list available in Appendix B), with a range of 7-32 outcomes per study and a median of 14. The majority of outcomes mapped to the COMET core areas of 'life impact' (n=73, 94%), with the remainder mapping to 'physiological/clinical' (n=3, 4%) and 'resource use' (n=2, 3%). The highest number of outcomes were identified in the COMET domain of 'delivery of care' (n=21, 27%), followed by emotional functioning/wellbeing (n=19, 25%), personal circumstances (n=16, 21%), cognitive functioning (n=14, 18%), social functioning

(n=3, 4%), need for further intervention (n=2, 3%), pregnancy, puerperium, and perinatal outcomes (n=2, 3%), and congenital, familial and genetic outcomes (n=1, <1%). At the most granular level, outcomes were grouped into 19 CODECS domains, with distributions of outcomes across studies shown in Figure 8.

Table 5: Characteristics of included studies

Descriptor	Number of Studies
Year of publication (N=16)	
2020-2016	9
2010-2015	7
Country of study (N=13*)	
Australia	3
Canada	1
Israel	1
The Netherlands	3
UK	2
USA	3
Population†	
Average risk (normal screening result)	5
Heterozygotes (one reproductive partner heterozygote for a recessive condition)	7
Increased risk couples (female partner heterozygous for an X-linked condition, or both partners heterozygous for a recessive condition)	5
Decliners of RGCS	2
Increased risk ethnic group before results available	1
RGCS results not disclosed (Dor Yesharim)	1
Intervention†	
Haemoglobinopathies	3
Targeted panel in founder population	5
Expanded carrier screening (ECS)	3
Cystic fibrosis (CF)	2
3-gene panel (CF, FXS, SMA)	2

*16 publications from 13 studies;†Some studies included multiple populations/interventions

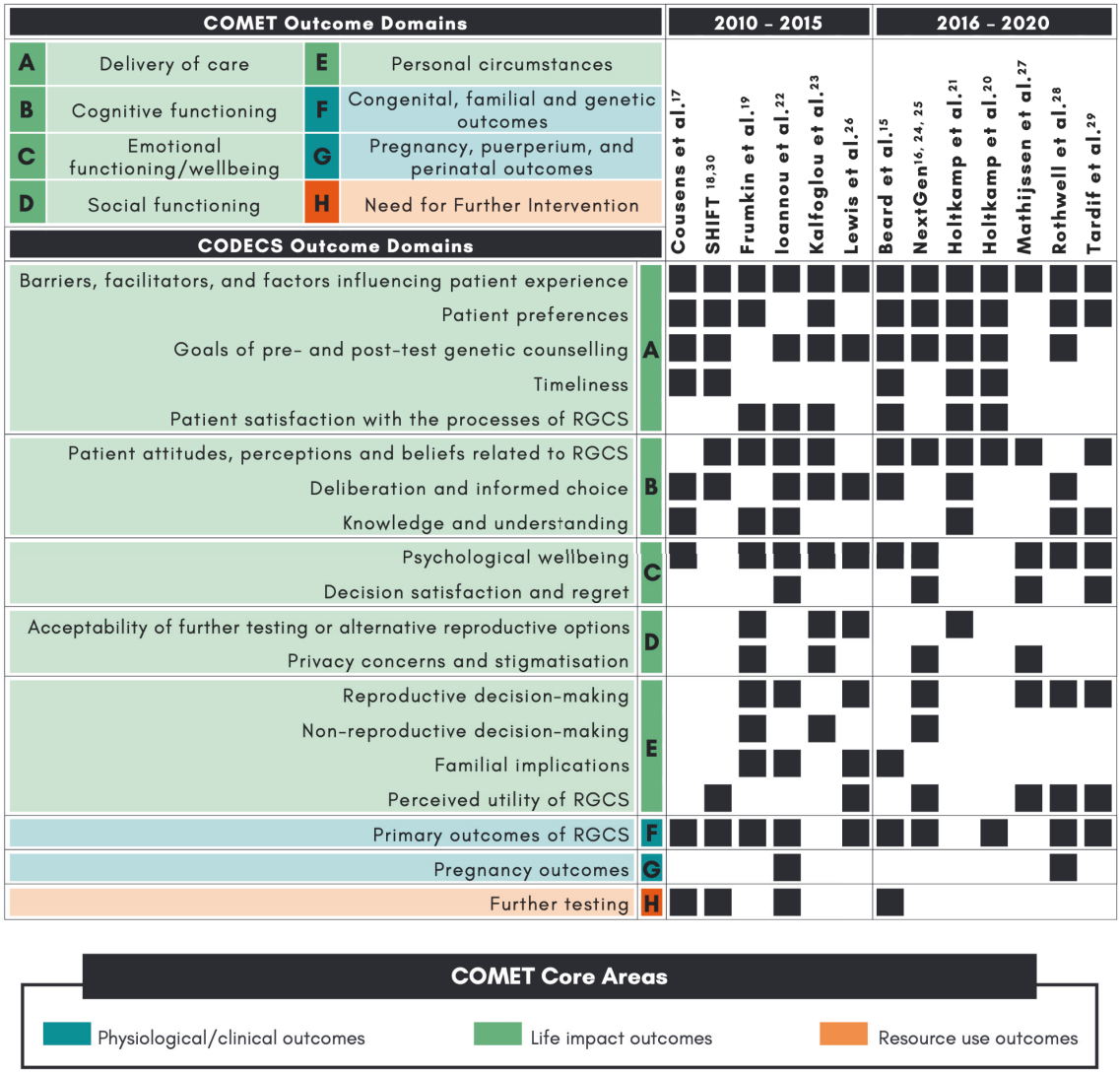

Figure 8: Outcomes domain across studies

COMET core areas indicated by colour, COMET Outcome Domains indicated by A-H, CODECS Outcome Domains as listed in full.

Delivery of care

Twenty-one outcomes related to the COMET domain 'delivery of care' and were grouped in the CODECS domains 'barriers, facilitators and factors influencing patient experience', 'patient preferences', 'goals of pre- and post-test genetic counselling, 'timeliness', and 'patient satisfaction with the process of RGCS'. All studies included quotes or themes related to 'barriers, facilitators and factors influencing patient experience' of RGCS, this was the only CODECS domain that was uniformly represented across all included studies. These outcomes were most frequently related to barriers and facilitators to uptake of RGCS, followed by factors influencing emotional reactions and psychological wellbeing of patients.

Of the outcomes that mapped to 'delivery of care', the greatest number of outcomes were grouped in the CODECS domain 'goals of pre- and post-test genetic counselling' which was identified in 10 studies. Quotes and themes that informed this domain reflect patient needs at pre-test and post-test timepoints and how well these are met, and can be broadly categorised into two groups. Firstly, outcomes related to information needs; including whether sufficient information was provided to meet patient needs, whether the timing and method of information provision promoted understanding, and whether the information provided supported informed decision-making. Secondly, outcomes related to providers of genetic counselling; including whether the provider was accessible, knowledgeable, presented RGCS as a choice, and was empathetic.

Emotional Functioning/Well-being

Nineteen outcomes related to the COMET domain 'emotional functioning/wellbeing' and were grouped in the CODECS domains 'psychological wellbeing' and 'decision satisfaction and regret'. Outcomes were associated with four timepoints; waiting for results, receiving results, undergoing further testing and prenatal decision-making, and long-term. The majority of these outcomes were in the CODECS domain 'psychological wellbeing' and were identified in 10 studies. A variety of emotional reactions were captured in the outcomes derived from included studies and where possible were extracted verbatim to demonstrate the different terminology used by patients in order to gain a better understanding of meaningful psychological outcomes to assess in this area. A range of illustrative words were used by patients to relay their emotional experience including anxiety, distress, fear, grief, relief, sadness, shock, sorrow, stress and worry. The most frequent psychological outcome was 'shock' (n=6), followed by 'anxiety' (n=4), and 'relief' (n=4). Many of the psychological outcomes identified in qualitative studies were also identified in quantitative studies, with the exception of grief which was unique to qualitative studies. Specific outcomes that relate to the experience of pregnancy following an increased risk result were also identified, including detachment from a current pregnancy, difficulty feeling happy to fall pregnant, and loss of spontaneity around conception.

Factors that influenced emotional wellbeing could be deduced from some studies and included feeling supported by a genetic counsellor[15], the strength of the couple's relationship and coping strategies[27], having sufficient pre-test information[17], and having a low pre-test perceived risk of an increased risk result[15,21,22,28,29].

Personal circumstances

Sixteen outcomes related to the COMET domain 'personal circumstances' and were grouped in the CODECS domains 'reproductive decision-making', 'non-reproductive decision-making', 'familial implications, and 'perceived utility of RGCS'. Outcomes in this domain related to how the personal circumstances of the individual, couple, or wider family were impacted by RGCS. How the results of RGCS influenced reproductive decision making was most frequently represented, being identified in 7 studies. Six studies included quotes or themes that reflected patients perceived utility of RGCS, which was characterised by two aspects. Firstly, utility was defined by the timeliness of results, with emphasis being placed on earlier results or preconception offers in order to allow sufficient time for consideration and decision making. Secondly, utility was reflected by patients' sense of confidence or empowerment in their reproductive decision.

4.5.5 Findings of the sequential review

The following results refer to the findings across all studies, both quantitative and qualitative, and provides a comparison of the outcomes that were identified.

Distribution of studies

Across both quantitative and qualitative systematic reviews of studies published between 2010-2020, we identified 77 publications from 57 studies. These included 14 publications from 4 mixed methods studies, 9 publications from 9 qualitative studies, and 54 publications from 44 quantitative studies.

Outcomes and domains

We identified 163 outcomes grouped into 26 CODECS domains. Sixteen domains were represented in both quantitative and qualitative studies, 7 domains were identified in quantitative studies only, and 3 domains were identified in qualitative studies only (Figure 9). The three CODECS domains that were newly identified in the qualitative review were 'goals of pre- and post-test genetic counselling', 'acceptability of further testing and alternative reproductive options', and 'perceived utility of RGCS'.

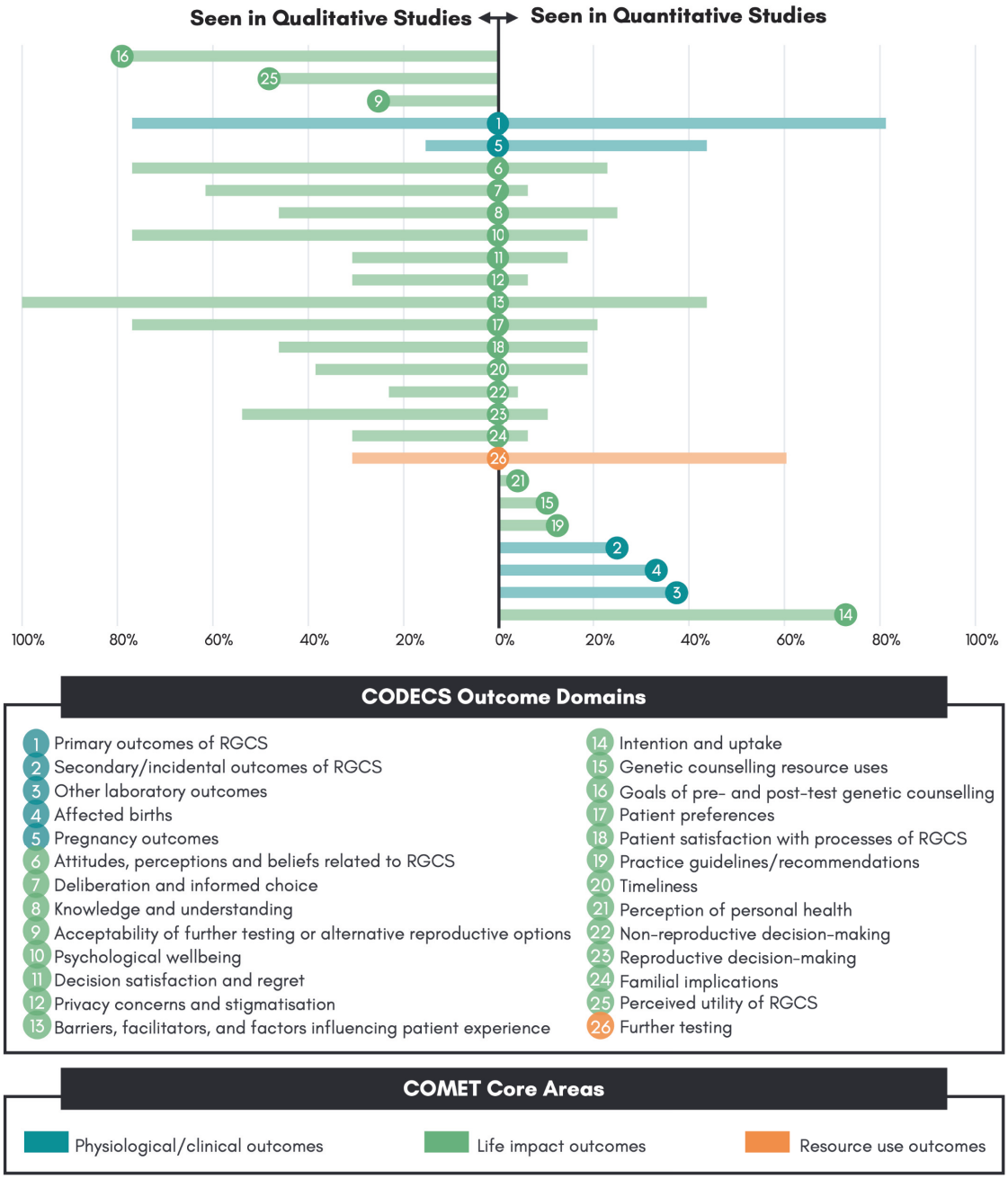

Figure 9: Proportion of studies reporting per CODECS outcome domains

Comparison between quantitative and qualitative studies

Left – outcome domains that were seen only in qualitative studies. Central – outcomes domains that were seen in both qualitative and quantitative studies. Right – outcome domains that were only seen in quantitative studies

Box 2: Comparison of key findings from sequential systematic reviews of quantitative and qualitative studies

Quantitative studies	Qualitative studies

• Indications of potential biases, including selective reporting bias, were identified
• Outcome heterogeneity and variability in measurement methods limited the ability to compare and combine findings across studies
• Outcomes had limited applicability to criteria used to evaluate genetic screening programs
• Patient perspective was lacking, with few studies including patient reported outcomes and no reported public and patient involvement in study design or conduct
• In order to work towards the goal of evidence-based practice, agreement on a standardised set of core outcomes that capture the benefits, harms and impact of RGCS is needed
	• Three outcome domains that were not previously represented in quantitative studies were identified in this review
	  ○ Goals of pre- and post-test genetic counselling
	  ○ Acceptability of further testing and alternative reproductive options
	  ○ Perceived utility of RGCS (composed of empowerment and timeliness)
	• Quotations provided clarification of psychological outcomes of RGCS and identified grief as an outcome that may be warranted in future studies
	• Many verbatim extracts from qualitative studies were negatively phrased, indicating that consideration should be considered to defining potential adverse outcomes in this setting

4.6 Discussion

This systematic review of qualitative studies identified outcomes of importance to patients accessing RGCS. The outcomes identified provide rich insights into the perspectives and needs of patients in relation to RGCS, and are valuable additions to the 'long list' of outcomes being considered for inclusion in a COS. Importantly, this review identified outcomes that were not identified in a previous published systematic review of outcomes measured in quantitative studies[5], with 3 new outcome domains being defined.

The first CODECS domain newly identified in the qualitative review was 'goals of pre- and post-test genetic counselling'. This domain captures outcomes related to the patient experience of pre- and post-test interactions with their health providers. Genetic counselling in this context can be performed by a range of health professionals, which may include genetic counsellors as specialised providers but often involves a range of other non-genetic health professionals. Outcomes in this domain reflect recognised goals of genetic counselling as defined by the Human Genetics Society of Australasia (HGSA) and the National Society of Genetic Counselors (NSGC), including the interpretation of family and medical history to assess chance of disease occurrence, education and counselling to promote informed choice, and support to encourage the best possible

adjustment to genetic information.[31,32] These outcomes also reflect criteria used to assess genetic screening programs broadly, such as aspects of voluntariness, accessibility, and the provision of good quality, comprehensible and balanced information.[33,34] The overlap of outcomes we identified, with these goals and criteria, highlights that these are not only outcomes that are needed to informed evidence-based practice recommendations at a procedural level but also practical considerations of importance to patients. Many of the direct quotes that informed outcomes in this domain reflected perceived inadequacies of the RGCS programs, for instance indicating that information needs hadn't been met, suggesting that there is room for improvement in the delivery of RGCS programs. There is a need for outcomes that reflect the goals of pre- and post-test genetic counselling to ensure that we capture whether patient needs are being met.

The second CODECS domain newly identified in the qualitative review was 'acceptability of further testing and alternative reproductive options'. This domain captures outcomes related to patients' perspectives on prenatal diagnosis, termination of pregnancy, and preimplantation genetic diagnosis. Personal preferences, religious and societal views, and practical difficulties were discussed in relation to these options. These concepts reflect contextual considerations around the implications of RGCS that are often not explored. Acceptability is a multi-faceted construct that reflects the extent to which people receiving a healthcare intervention consider it to be appropriate, and which encompasses both anticipated (prospective) and experienced (retrospective) aspects.[35] Acceptability as a concept is represented in quantitative studies of RGCS largely via uptake, with the assumption that if services are utilised then they are acceptable to patients. However, this does not account for the complex processes that can surround acceptability, nor does it consider retrospective acceptability once patients have lived experience of the process. It is evident from the identification of acceptability relating specifically to further testing and alternative reproductive options that acceptability beyond uptake would be valuable to explore in this setting. It is also important to recognise that all healthcare decisions are made within a societal context, and external influences can have significant impacts on the patient experience. The social impacts of RGCS are under-explored and measuring outcomes related to the social context in which decisions around RGCS, further testing, and reproductive decisions are made warrants further investigation, especially as RGCS becomes increasingly accessible to the general population.

The final CODECS domain newly identified in the qualitative review was, 'perceived utility of RGCS'. This domain captures outcomes related to patients perceptions of the impact of RGCS and how they utilised the results. Two components of utility were identified from qualitative studies; that results instilled a sense of confidence and empowerment related to reproductive decisions, and that utility was dependent upon results being available in a timely manner that allowed for consideration and decision-making. When considering utility, we must consider the aims of RGCS programs and how these can be operationalised as measurable outcomes. Whilst there is no consensus definition of the primary aim of RGCS, there are two aims that are often stated; to support reproductive autonomy through the provision of information regarding reproductive risk in order to allow couples' to make informed decisions regarding family planning, and to reduce the incidence of genetic conditions.[36,37] In our review of quantitative literature, utility was reflected in outcomes such as reduced birth rate, as well as intended and actual reproductive behaviours of those identified as increased risk. Timeliness was also represented in some quantitative studies, with utility being compromised if there was insufficient time for deliberation and decision-making. Whilst in our review of qualitative studies, we identified reproductive empowerment and timeliness as two components of patients' perceived utility of RGCS. Combining the findings of these sequential systematic reviews of outcomes in RGCS, it is evident that a consensus definition of the clinical utility of RGCS would be valuable and should consider aspects of empowerment, timing and reproductive decisions in order to reflect the clinical utility of RGCS in future studies.

A high degree of outcome heterogeneity was identified in the domain of 'psychological wellbeing' in our review of quantitative studies, with variability in the selection of outcomes and measurement methods that has limited the ability to compare psychological wellbeing across RGCS programs and hindered clear demonstration of benefits or potential harms. In this review we anticipated that direct quotations and themes from qualitative studies would provide greater insight into appropriate psychological outcomes to consider. Most notable was the outcome of grief, which was not seen in quantitative studies, but was represented in a number of qualitative studies. Grief was reflected in terminology such as 'sorrow' and 'great sadness', and encompassed multiple timepoints including the post-test period when individuals were identified as increased risk, when undertaking further testing and making decisions about a current pregnancy, and long-term when working towards a healthy pregnancy. We can look to

examples from obstetrics and fertility settings, where work has been done in assessing grief, to consider appropriate measures that could be utilised in studies on RGCS. Grief related to pregnancy loss including early miscarriages through to later term and postnatal losses, in addition to grief related to unsuccessful fertility treatments, have similarities to the journey of increased risk couples identified through carrier screening, whereby the journey to a healthy pregnancy may take a more difficult and medicalised path than traditional natural conceptions. Validated measurement tools are available to assess perinatal grief and may be suitable to adapt to the carrier screening setting.[38] It is important to acknowledge that the goal of assessing grief in this setting relates to potential adverse outcomes of RGCS, a rigorous understanding of which is needed to inform evidence-based practice recommendations and ensure that appropriate supports are in place for those that may experience complex grief following RGCS.

Whilst we did not categorise outcomes as adverse in this review, it was evident from the literature that many of the verbatim excerpts reflected perceived inadequacies of RGCS programs. For example, many of the goals of pre-test counselling were not met, most often in regards to information provision but also encompassing aspects such as timing of service delivery, presenting RGCS as a choice, feeling that decision-making was informed and that implications of testing were understood. Routinisation of genetic testing and whether the goal of truly informed choice is achievable has been explored in the setting of prenatal testing, and likely will have relevance for RGCS as it becomes a mainstay of preconception and early prenatal care.[39-41] Negative experiences in the form of grief and regret were also identified. There is currently no consensus definition of adverse outcomes from genetic testing. Identification of these is crucial for ensuring patient wellbeing, and initial analysis would suggest that adverse outcomes can be minimised in various ways. For example, regret may be related to feeling uninformed or that testing was not voluntary, leading to a lack of ownership over the decision to have testing. The nature of RGCS means that grief is likely to play a role in many cases, however complex grief may be minimised by providing appropriate supports throughout the process and identifying those at-risk that may require additional resources. Definition of adverse outcomes will be an important element to consider in the development of a COS. It is crucial to understand if individuals who undertake RGCS are at risk of complicated or prolonged grief or have unmet genetic counselling needs in order to consider how this can be minimised and used to inform implementation of RGCS.

The risk of bias associated with qualitative studies in this review identified some areas of consideration when interpreting findings. Overall mean quality assessment scores indicate potential risk of bias in this body of literature, consistent with findings in our review of quantitative studies. Of particular note, no studies reported a reflexive account of potential influences of the researcher or study methods on their findings. There are varied arguments for the necessity of reflexivity in qualitative research, however it is broadly agreed that consideration of researcher influence is an important element of rigor.[42,43] In this context, the absence of reflexivity limits the transparency of these studies. Crucial points at which bias may be introduced in research include definition of study aims, interview guides and questions asked of participants, and interpretation of themes from the resulting data. If not accounted for, the perspective of researchers and clinicians involved in the study may skew the data towards their goals. We acknowledge that many studies incorporated aspects such as co-coding into their study design which illustrate that researcher positioning and influence were considered, however have not been transparently reported. Practical limitations such as word counts in journal articles are also acknowledged, however in accordance with the COREQ guidelines for reporting of qualitative studies we suggest that a concise statement to summarise that reflexivity has been considered should be a minimum expectation in the reporting of future qualitative studies.[44]

Using qualitative methods to explore patient experience can be a valuable tool to identify outcomes that are relevant to patients and ensure that research findings have direct translational impact on clinical practice.[45] Of the qualitative studies that were reviewed, only one paper by Lewis et al. explicitly aimed to identify outcomes.[26] This study applied a grounded theory approach to interviews conducted with individuals who had undergone RGCS, and identified reproductive empowerment as the main motivator and outcome of carrier screening. As previously mentioned, quantitative studies also lacked involvement of patients in the definition of research outcomes, with no reports of patients involved in the design of studies and selection of outcomes, and few studies utilised patient-reported outcomes. This limited representation of the patient perspective in regards to outcomes that are relevant and informative in this setting, across both quantitative and qualitative studies of RGCS, indicates that the real world needs and concerns of patients undertaking RGCS may be under-represented in current literature. Despite Lewis et al. providing the first example of a qualitative study aimed at identifying a key outcome of RGCS, no subsequent published studies of RGCS have reported

empowerment as an outcome. A patient-reported outcome measure based on the concept of empowerment has been developed for use in clinical genetics services, with broad uptake internationally, including translation into a number of other languages and adaptation into a short-form version for ease of use.[46–49] Whilst adaptation to some items would be needed, this validated patient-reported outcome measure could be a valuable addition to future studies on RGCS. Primary qualitative research to elicit outcomes of importance, as planned as a component of the CODECS study, will also ensure that outcomes relevant to patients are included in future research.

Based on the number of qualitative studies included in this review, it is evident that researchers and clinicians are cognizant of the benefits of understanding patient experience and have appropriately used qualitative methods as an exploratory step to capture the patient perspective of RGCS. However, the translation of these exploratory findings into patient-centred outcomes that can be routinely incorporated into studies evaluating RGCS programs is needed. This review has identified a number of areas for future research, many of which will be addressed within the scope of the CODECS study. Stronger representation of the patient perspective is needed to ensure that RGCS is conducted in a people-centred manner. Public and patient involvement should be considered at the inception of research design, and researchers should strive to select patient-reported outcomes that have been developed using an evidence-base involving patients. Once complete, a COS will provide clear, evidence-based guidance for which outcomes should be measured as the starting point for all future studies of RGCS. Generalisability is also a consideration for future research. Compared to quantitative studies which were identified in 15 countries, qualitative data was only available for 6 countries. Future research should aim to incorporate international patient representation, or consider to what degree outcomes are likely to significantly differ across countries.

4.7 Limitations

Publications not available in English were excluded due to a lack of resources for translation. The deductive method used to extract outcomes from qualitative studies holds some inherent limitations, including that the influence of the researcher(s) conducting the data extraction could alter the meaning within text excerpts due to unconscious knowledge or biases. This was recognized and minimized through the double coding and review of all coded excerpts, as well as grouping within outcome domains by a second reviewer and the wider study management group. Some limitations exist in the

generalisability of the outcomes identified in this review. Qualitative studies included representation from 6 countries, predominantly of White/European populations, which is significantly less diverse than quantitative studies which included 15 countries. Within the 6 countries, demographics are further skewed towards high socioeconomic groups. Only 3 studies were in groups that had accessed expanded carrier screening panels, and as this is becoming increasingly the standard over small or ethnicity-based panels, further qualitative exploration in groups accessing large panels may be warranted to ensure all relevant outcomes are captured. Therefore, caution must be taken in assuming that the range of outcomes identified in this review would be generalizable to all populations. In accordance with the aims of the CODECS study, further work is underway to ensure that diverse patient perspectives are incorporated in the development of the core outcome set.

4.8 Conclusion

This review identified outcomes that are important to people who access RGCS and will inform the development of a COS for population-based RGCS. We identified a number of outcomes that were not previously represented in quantitative studies, indicating that this review constitutes an important step in ensuring that the patient perspective is strongly represented in future stages of the CODECS study.

4.9 Summary of supporting data available in Appendix B

The following supporting data are available in Appendix B:

Supplementary material B.1 – Illustrative search strategy

Supplementary material B.2 – COMET/CODECS taxonomy version 1.1

Supplementary material B.3 – Summary of included studies

Supplementary material B.4 – Risk of bias assessment

Supplementary material B.5 – List of outcomes extracted from qualitative studies

Supplementary material B.6 – Block diagram of outcomes reported per study

4.10 References

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Chapter 5: Stakeholder consultation

5.1 Chapter overview

In this chapter, I present the findings from patient stakeholder consultations that were conducted to fill a gap in knowledge regarding the outcomes of importance to patients undertaking reproductive genetic carrier screening.

This chapter is structured per the corresponding published journal article followed by additional content relevant to the qualitative methods used.

> Richardson E, McEwen A, Newton-John T, Crook A, Jacobs C. Outcomes of importance to patients in reproductive genetic carrier screening: A qualitative study to inform a core outcome set. *J Pers Med.* 2022;12(8):1310. doi: https://doi.org/10.3390/jpm12081310

5.2 Abstract

There is significant heterogeneity in the outcomes assessed across studies of reproductive genetic carrier screening (RGCS). Only a small number of studies have measured patient-reported out-comes or included patients in the selection of outcomes that are meaningful to them. This study was a cross-sectional, qualitative study of 15 patient participants conducted to inform a core outcome set. A core outcome set is an approach to facilitate standardisation in outcome reporting, allowing direct comparison of outcomes across studies to enhance understanding of impacts and potential harms. The aim of this study was to incorporate the patient perspective in the development of a core outcome set by eliciting a detailed understanding of outcomes of importance to patients. Data were collected via online, semi-structured interviews using a novel method informed by co-design and the nominal group technique. Data were analysed using reflexive thematic analysis. Outcomes elicited from patient stakeholder interviews highlighted several under-explored areas for future research. This includes the role of grief and loss in increased risk couples, the role of empowerment in conceptualising the utility of RGCS, the impact of societal context and barriers that contribute to negative experiences, and the role of genetic counselling in ensuring that information needs are met and informed choice facilitated as RGCS becomes increasingly routine. Future research should focus on incorporating outcomes that accurately reflect patient needs and experience

5.3 Graphical abstract

5.4 Introduction

Reproductive genetic carrier screening (RGCS) is a genetic test that allows prospective parents to determine if they are at increased risk of having a child with a recessive genetic condition, facilitating informed decision-making regarding how to proceed with their family planning. RGCS can range in complexity from haemoglobinopathy screening in routine prenatal care, through to expanded carrier screening of hundreds to thousands of genetic conditions in preconception or prenatal settings. Current consensus-derived practice guidelines recommend that RGCS is offered to all women planning a pregnancy or in their first trimester [1-3]. In a previous sequential systematic review of quantitative and qualitative studies on RGCS, we highlighted the heterogeneity of research to date and identified a need for standardised outcome reporting to inform evidence-based practice recommendations that can draw on a robust underlying literature [4,5].

The Core Outcome Development for Carrier Screening (CODECS) study aims to develop a core outcome set (COS) for studies on RGCS.[6] A COS is a minimum set of outcomes that should be measured and reported in all studies on a particular topic. There are three key stages of COS development; (i) reviewing current evidence, (ii) consulting with key stakeholders, and (iii) a consensus process to decide which outcomes are prioritised for inclusion. The CODECS study aims to ensure the perspectives of patients are strongly represented in the development of a COS. Previous COS studies on other topics have demonstrated that the inclusion of patients in a consultative process results in outcomes that would not have been suggested by health professionals alone [7,8]. They demonstrate that incorporating qualitative methods ensures that outcomes are meaningful for patients, provides a deeper understanding of why outcomes are valued and how they are prioritised by patients, guides the scope and language used to describe outcomes, and allows comparison of patient-derived outcomes with those from other sources such as systematic reviews [8].

Qualitative research in the development of core outcome sets is evolving, and there is currently limited guidance on best methods to utilise. A key challenge is how to approach eliciting outcomes with lay stakeholders, who may be unfamiliar with this concept [8]. A summary of available guidance and how this informed our methodological choices is available in Appendix C. Drawing on examples from the literature and utilising the theoretical frameworks of co-design and nominal group technique, we developed a novel approach to eliciting outcomes of importance to patients [9-11]. Co-design allows users to become part of the design team as 'experts of their experience' [12]. While many

COS studies have shown the value of co-design with patients, few have expanded on how best to utilise co-design principles to engage with patients when eliciting outcomes to include in the consensus process. Nominal group technique is a structured process used to achieve consensus amongst small groups [9,10]. We adapted key aspects of the nominal group technique for application in one-on-one interviews, including initial generation of ideas by participants without input or prompting from the interviewer, recording and discussion of each idea through a shared medium (virtual whiteboard), and prioritisation of ideas by participants. This structured approach allowed participants to produce descriptions of their experience in a way that enabled conversion into measurable outcomes.

This study reports on the results of qualitative interviews with patient stakeholders designed to elicit outcomes of importance to prospective parents accessing RGCS. The outcomes identified herein will be added to the 'long list' of outcomes collated from previous systematic reviews, and taken forward to the consensus process to determine which outcomes should be defined in a core outcome set for RGCS. This study has two aims:

Aim 1: To explore the themes underlying participant interviews and how these inform our understanding of outcomes that are important to prospective parents accessing RGCS

Aim 2: To explore the role of including qualitative consultation with patient stakeholders in the development of a COS.

5.5 Materials and methods

This study was reported according to the consolidated criteria for reporting qualitative research (COREQ).[13] Ethics approval was granted by the University of Technology Sydney Ethics Committee (UTS HREC ETH20-5179).

5.5.1 Theoretical paradigm

We approached this study through a constructivist paradigm, where the interaction between the researcher and participant, and the influence that has on the resulting data, is viewed as an essential component that drives the co-creation of knowledge [14]. To engage in self-examination and consider how the researcher's knowledge, assumptions or biases influenced the data collection, ER wrote reflective notes after each interview and throughout the analysis process.

5.5.2 Recruitment and patient and public involvement

Individuals or couples who accessed RGCS to inform their reproductive decisions were eligible to participate in this study. For the purpose of this study, individuals and couples undertaking RGCS will be referred to as patients, however we acknowledge that these will be largely healthy adults, most of which will not go on to require significant medical follow-up as a result of their carrier screening results. Participant groups were defined by two characteristics: their level of risk prior to RGCS (*a priori*) and their level of risk following results (*a posteriori*). Average *a priori* risk was defined as the participant having no existing health concerns or family history to indicate an increased risk of being a carrier. Increased *a priori* risk was defined as the participant having an existing factor such as ethnicity with a known increased carrier frequency or a known family history of a recessive genetic condition. *A posteriori* risk was grouped into either low or increased reproductive risk. Low reproductive risk results were defined as those where neither member of a reproductive couple were found to be carriers of the same genetic condition, or where one member of a reproductive couple was found to be a carrier of an autosomal recessive genetic condition but their reproductive partner was not a carrier of the same condition. Increased reproductive risk results were defined as those where both members of a reproductive couple were found to be carriers of the same autosomal recessive genetic conditions, or where the female reproductive partner was found to be a carrier of an X-linked recessive genetic condition.

Different outcomes were expected to arise between participants based on their *a priori* and *a posteriori* risks, as well as the setting and context within which they accessed RGCS. As such, we utilised a broad passive social media approach to recruit a diverse international sample of participants with a range of RGCS experiences to capture a variety of outcomes to consider for inclusion in a core outcome set. An expression of interest to participate in the research was circulated through online parenting forums, Twitter, and a Facebook group for carriers of genetic conditions. Respondents were directed to a brief survey to confirm eligibility, provide contact information, and indicate if they would prefer to participate in a one-on-one interview, focus group, or did not have a preference. Once eligibility was confirmed participants were contacted via email and a meeting time arranged.

5.5.3 Inclusion and exclusion criteria

Individuals and couples were eligible to participate if they spoke English, had undertaken RGCS and received a result. Those who had not yet received results were excluded. Health professionals were excluded to ensure that data reflected lay experiences.

5.5.4 Participant selection

Purposive sampling was used, aiming for equal representation across *a priori* and *a posteriori* groups, and diverse international representation. We approached sample size through the lens of recent commentaries that highlight the problematic nature of aiming for "saturation" as an end-point for recruitment [15,16]. We instead adopted the concept of theoretical sufficiency, which seeks the point at which the researcher has sufficient depth of understanding to address the study aims [15]. In the context of this core outcome set development study, theoretical sufficiency was represented as the point at which a range of patient experiences that encapsulated outcomes of importance were captured. The goal was not to identify all possible outcomes, but rather those of most importance that warrant consideration for inclusion in a core outcome set. Data collection and analysis were performed concurrently. Data collection ceased when sufficient richness of information was achieved.

5.5.5 Data collection

Semi structured interviews were conducted remotely via Zoom [17] by ER between June and October 2021. Interviews were audio- and video-recorded. Basic demographic information was collected at the beginning of interviews. We used recent guidance on reporting race and ethnicity in medical and science journals to define categories based on participant's self-reported ethnicity [18]. We developed an interview schedule that engaged participants in a discussion about their experience and allowed them to conceptualise outcomes that were appropriate to capture it. The interview guide was informed by our sequential systematic review [4,5] and developed iteratively with two patient representatives (available in Appendix C). The interview guide was broken into four sections, becoming increasingly specific as the interview progressed (Figure 10).

1. Narrative exploration - participants were asked open questions about their uptake of RGCS and prompted to tell the story of their experience.
2. Word association exercise - participants oriented themselves within the narrative they had just described and wrote down words that came to mind to

describe their experience. The RGCS process was divided into 4 time-frames; pre-test counselling and deciding to access RGCS, waiting for results, receiving results and the immediate follow-up period, and the long-term perspective. Participants used pen and paper to record their words for each time-frame and were given up to 5 minutes to write down as many words as they could think of. A blank virtual whiteboard was shared with each participant and their chosen words were recorded. An illustrative example of the virtual whiteboard completed during an interview is available in Appendix C.

3. Exploration of generated words and eliciting of outcomes - participants expanded on each word they had written, and why they thought that word had come to mind. Through this exploration, the interviewer guided the participant in conceptualising how these words could be converted into measurable research outcomes. An example was shared with participants to facilitate their understanding of the notion of outcomes and how to convert their word association into measurable outcomes.
4. Prioritisation exercise - participants considered the outcomes they had discussed with the interviewer and their importance, ranking the top 3 that they considered crucial for research to explore.

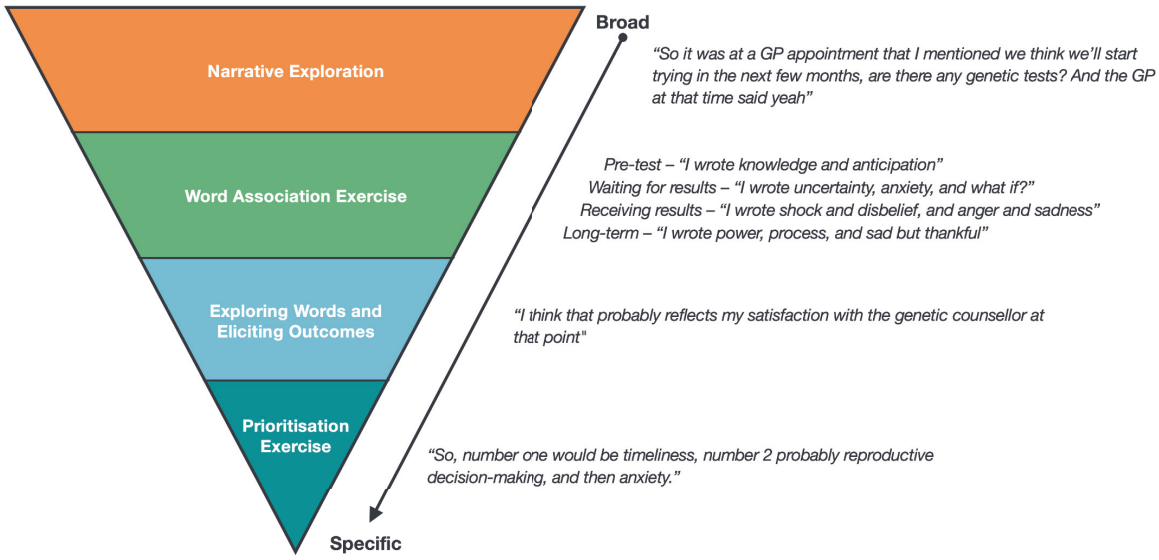

Figure 10: Interview schedule overview with examples

5.5.6 Data analysis

Interviews were transcribed verbatim and analysed using reflexive thematic analysis [19]. The transcripts were not returned to participants for corrections, as this was deemed unnecessary due to the collaborative process of the interviews. ER and CJ independently coded two transcripts and compared and discussed codes. ER then coded the remaining interviews. CJ reviewed the codes for the remaining interviews and discussed the approach and reasoning behind the codes. Data was stored and managed using NVivo software [20].

An inductive approach to coding was adopted, initially utilising semantic codes that closely reflected the participants' own words. Codes were developed iteratively and those with close semantic similarity were merged and associated with an overarching outcome code. The virtual whiteboard generated with each participant during their interview was compared to the codes derived from their transcript to ensure that all elicited outcomes had been captured.

We used a deductive approach to map the outcomes to an existing taxonomy previously developed for this study (available in Appendix C), and to an overarching taxonomy defined by the COMET initiative [21]. This analysis resulted in a list of outcomes that were elicited from patients, grouped into outcome domains, that was directly comparable to outcome domains reported in a previous sequential systematic review [4,5]. Outcomes were collated to determine a final long list that would be included in the consensus process for development of a core outcome set, and assessed for outcomes that were uniquely identified by patients in this study.

Outcome domains were analysed to develop themes to answer the question "which outcomes of RGCS are most important to patients, and most accurately capture their needs and experience?". Illustrative quotes are denoted by study ID, reproductive risk, setting of RGCS access, and country of residence.

5.6 Results

5.6.1 Participant characteristics

The majority of participants (n=10) that responded to the EOI indicated a preference for one-on-one or couple interviews, while the remainder had no preference (n=5), For consistency, and due to time-zone complexities, it was decided that all participants would be interviewed as opposed to convening a focus group. Interviews were conducted with 15 participants (9 individual interviews, and 3 couple interviews). The majority of

participants were female (n=12, 80%), and all males participated in a couples interview with their partner. Due to the social media approach utilised for recruitment, non-participation was unable to be assessed. The average interview duration was 61 minutes (range 38-84 minutes). The mean age of participants was 32 (range 25-46). All participants had undergone RGCS within the last 5 years. Table 6 describes the sample characteristics.

Table 6. Characteristics of interview participants

Descriptor	Number of Participants
Gender (n=15)	
Female	12 (80%)
Male	3 (20%)
Country (n=12)	
Australia	4 (33%)
Canada	1 (8%)
New Zealand (NZ)	2 (17%)
UK	1 (8%)
USA	4 (33%)
Self-reported ethnicity (n=15)	
Ashkenazi Jewish	2 (13%)
Black African	1 (7%)
European New Zealand	2 (18%)
Multiracial (Hispanic, White and Native American)	1 (7%)
Multiracial (Aboriginal and Torres Strait Islander, White)	1 (7%)
White	8 (53%)
Highest level of education (n=15)	
Vocational	2 (13%)
Tertiary - undergraduate	4 (27%)
Tertiary - postgraduate (Masters or PhD)	9 (60%)
Timing of RGCS (n=12)	
Prenatal	2 (16%)
Preconception (proactive screening)	5 (42%)
Preconception (following fetal loss)	5 (42%)
Type of RGCS (n=12)	
Expanded RGCS	11 (92%)
Midwife-led haemoglobinopathies screening	1 (8%)
Risk group (n=12)	
Low risk (no carrier findings)	1 (8%)
Low risk (one reproductive partner heterozygote for an autosomal recessive condition)	3 (25%)
Low risk (FXS premutation carrier with <1% risk of expansion)	1 (8%)
Increased risk couples identified through RGCS[a]	2 (16%)
Increased risk couples identified following fetal loss[b]	5 (42%)

a - female partner heterozygous for an X-linked condition, or both partners heterozygous for an autosomal recessive condition; b- no additional carrier findings on expanded RGCS

5.6.2 Aim 1: To explore the themes underlying participant interviews and how these inform our understanding of outcomes that are important to prospective parents accessing RGCS

Four core themes were identified from participant interviews: the importance of pre- and post-test genetic counselling for patient experience, psychological wellbeing in increased risk couples, challenges and barriers facing patients, and perceived utility of RGCS from the patient perspective. These themes highlight outcomes of RGCS that are most important to patients and which may warrant focus in future research.

Theme 1: The importance of pre- and post-test genetic counselling for patient experience

For the purpose of this study, genetic counselling is considered a communication process that can be performed by a range of health professionals including GPs, midwives, obstetrician gynaecologists and maternal fetal medicine specialists, as well as specially trained genetic health professionals such as genetic counsellors and clinical geneticists [22]. All participants described pre- and post-test genetic counselling with their health provider as a crucial aspect of their RGCS experience and identified a number of key goals health providers should strive for.

All participants discussed the role of genetic counselling in promoting a sense of reproductive empowerment, by facilitating the provision of information regarding reproductive risk and assisting with the comprehension and understanding of the implications of results.

> "*Receiving results was two-fold; it was feeling informed and empowered by being informed.*"
>
> – ID-9, increased risk couple, RGCS following fetal loss, Canada

Participants discussed their perception of whether information needs had been met at various stages throughout the RGCS process. Many thought that there was room for improvement in pre-test genetic counselling to ensure that patients adequately understand what RGCS is and the possible implications of results.

> "*I would say I was half informed, like I think that our doctor and the representative from the testing place…could have done a little bit of a better job explaining exactly what was being tested for.*" – ID-1, increased risk couple, proactive RGCS in the prenatal setting, USA

Others found genetic counselling to be informative and that their needs were met.

> "*We had really good communication from the genetic counsellor who handled everything…they were really thorough with how they explained everything.*" – ID-10, low risk couple, proactive RGCS in the preconception setting, Australia

Participants commented on the importance of feeling supported and understood during genetic counselling.

> "*We had the call for the results and we were able to ask questions there, but then she also gave us her email and said if you do have any questions just send us an email and yeah, so it was very supportive.*" – ID-4, low risk couple, proactive testing in the preconception setting, Australia

Nuances of different settings were apparent, with participants who accessed RGCS as part of an IVF work up or through midwifery screening programs in routine prenatal care commenting that more information was needed.

> "*I think in general they should maybe sit down with you at the start, even with a pamphlet and just let you know [the details]... I think that at the start, it would be better if they just were a bit clearer.*" – ID-3, low risk couple, RGCS in the IVF setting, NZ

Making an informed choice was also discussed by participants who accessed RGCS in IVF or routine prenatal care settings. In these settings screening was experienced as less of a choice and participants put trust in their healthcare providers to decide what testing was appropriate.

> "*It almost wasn't really given as a choice for genetic testing for us, the doctor kind of just was like 'you guys should do this', and we were like' okay if you say so'. It wasn't a 'we want to do this', it was 'you should do this… Yeah, and you trust your doctor to know what they're recommending to you, and just say OK great.*" – ID-1, increased risk couple, proactive RGCS in the prenatal setting, USA

While many types of information were discussed, practical information about next steps when receiving an increased risk result were a focus for many participants, with some noting that they weren't equipped with all the information they needed.

"*Most of all is I want to know what my plan is now and I don't think I had information on providers in the future and like what they do, what the process needs to look like if I want a natural route or an IVF route, like, I had to figure out all of that on my own, like I said, I still don't fully comprehend exactly all the providers that I need to touch on if I went for a natural pregnancy.*" – ID-8, increased risk couple, RGCS following fetal loss, USA

Theme 2: Psychological wellbeing in increased risk couples

Nine participants, including two couples, faced an increased reproductive risk when planning future pregnancies and provided insight into the long-term psychological impact of an increased risk result. Participants described grieving the loss of an expected pregnancy journey, and those who had also experienced a fetal loss were able to recognise an evolution from grieving the loss of a child to a prolonged grieving of their expected future.

"*So you weren't even losing the pregnancy and your child, but you're losing all the stuff you'd mentally planned for…it's a lot more than just grieving a child or the baby, it's the whole life that you'd kind of dreamed up.*" – ID-12, increased risk, RGCS following fetal loss, NZ

Medicalisation of the journey to a healthy pregnancy was described by many participants, whether they accessed IVF with PGD or conceived naturally and undertook prenatal diagnosis; in all instances participants described the loss of spontaneity and joy around early pregnancy.

"*It's gone from trying to conceive naturally, which was very fun, to IVF which is very not fun.*"

– ID-2, increased risk couple, proactive RGCS in the preconception setting, Australia

The loss of time leading to the goal of a healthy pregnancy was also a source of grief for several participants.

"*There's the loss of what we thought was, you know, 'the' pregnancy and then loss of time… in my mind, I'm thinking and processing the fact that like we're ready to start our family, but there's still so many steps to take before that.*" – ID-1, increased risk couple, proactive RGCS in the prenatal setting, USA

Theme 3: Challenges and barriers facing patients

When relaying their experience of accessing RGCS, all participants discussed barriers that negatively affected their experience. Many participants found it challenging to navigate the practical aspects of access and the complexities of the social context in which RGCS takes place.

Cost and convenience of the process were frequently discussed, and how these may lead to a more motivated and higher socioeconomic group accessing RGCS.

> "*Because yeah, there's quite a big cost to all this testing as well in New Zealand and our obstetric care is public funded for the midwife system and so people don't expect to pay a cent... when these opportunities aren't offered or only offered at a cost, suddenly this rich versus poor barrier is put in place.*" – ID-12, increased risk couple, RGCS following fetal loss, NZ

A small number of participants felt that their provider had struck a balance with cost and convenience that facilitated their uptake of screening.

> "*Yeah, I think accessibility is the biggest thing. Like for example, most people would [look up] genetic tests and just click the first result and see $1500 and a big pdf where you have to go to the doctor and do that, do this. It's just too much effort. Whereas [the test we accessed] is a lot more compelling...and affordable... you know in this on demand generation, order online, spit in this tube, and send it back and everything is done online, that is really good.*" – ID-11, low risk couple, proactive testing in the preconception setting, Australia

Many wished that there was more awareness of RGCS to facilitate it being offered to them preconception, and supported this being a priority in the future.

> "*The regret is that we waited so long to start the process of finding out the disorder. And then you know maybe we would have done that before [the affected pregnancy] had it been offered.*" – ID-1, increased risk, proactive RGCS in the prenatal setting, USA

Social barriers and stigmatisation were a focus for many increased risk couples, highlighting a need for research and recognition of the social context in which patients are experiencing RGCS in order to be prepared for the challenges they may face.

"*I feel more guarded about telling people that I'm expecting again. Because on either end there's judgement.*" – ID-9, increased risk couple, RGCS following fetal loss, Canada

Theme 4: Perceived utility of RGCS from the patient perspective

All participants identified reproductive empowerment as the key outcome that represented their perceived utility of RGCS.

"*Knowledge is power…by having that knowledge you've got the power to, and the confidence, to make future decisions without having really any worry in terms of genetics. There's always obviously random variations but in terms of on paper, I feel empowered.*" – ID-11, low risk couple, proactive testing in the preconception setting, Australia

Reproductive empowerment was a concept that was expressed regardless of risk, with increased risk couples feeling empowered to explore options, and low risk couples feeling empowered to proceed with natural conception.

"*That was as good as it could have been pretty much…I'm just happy that we could start planning and all that fun stuff…move forward without making any major changes to our plans.*" – ID-10, low risk couple, proactive RGCS in the preconception setting, Australia

The ability to inform reproductive decisions was also perceived as a key outcome of RGCS by most participants and was conceptualised as being complementary to their feelings of empowerment.

"[*The results] allow us to make data-backed or logical decisions for future pregnancies…we know we have three out of four shots of having a healthy pregnancy and so for us, compared to the IVF route, I feel like we can make decisions as long as they align with our emotional wellbeing to move forward with trying to conceive a healthy child naturally.*" – ID-6, increased risk couple, RGCS following fetal loss, USA

5.6.3 Aim 2: To explore the role of including qualitative consultation with patient stakeholders in the development of a COS

Word exercise and eliciting outcomes

Participants generated an average of 13 words (range 8-16) during the word association section of the interview. Through exploration of each word, an average of 16 outcomes

(range 11-32) were elicited from each interview. In total, 55 unique outcomes were identified across the 15 interviews. Thirty-seven of these outcomes overlapped with outcomes identified from our previous sequential systematic reviews of quantitative studies [4] (n=8), qualitative studies [5] (n=13), or both (n=16); and 18 were new outcomes.

In the twelve interviews that were conducted, the most frequent outcomes were 'genetic counselling promoted reproductive empowerment' (n=12, 100%), 'patient-reported confidence/empowerment related to reproductive decisions' (n=12,100%), 'factors influencing access and uptake of RGCS' (n=9, 75%), 'genetic counselling provided sufficient information to meet patient needs' (n=9, 75%), 'patient-reported anxiety' (n=9, 75%), 'pre-test perceived risk of a carrier finding' (n=7, 58%), and 'grieving the loss of an expected pregnancy journey and medicalisation of future pregnancies in increased risk couples' (n=7, 58%). These outcomes are informed by and correspond to the previously described themes generated from this study.

Outcome domains

Outcome domains, hereafter referred to as CODECS domains, were previously defined during data analysis for our sequential systematic review [4,5]. Definition of the domain and grouping of outcomes were developed iteratively by ER and AC and taken to the study management group (CJ, AM, TNJ) for final review and consensus. Twenty-six CODECS domains were defined.

Outcomes from this qualitative study mapped to 18 CODECS domains (Figure 11). All outcomes mapped to existing CODECS domains; therefore, no new outcome domains were identified. Nine overarching COMET taxonomy outcome domains were represented; delivery of care (n=12, 100%), cognitive functioning (n=12, 100%), emotional functioning/wellbeing (n=10, 83%), social functioning (n=7, 58%), personal circumstances (n=7, 58%), need for further intervention (n=6, 50%), pregnancy, puerperium and perinatal outcomes (n=5, 42%), congenital, familial and genetic outcomes (n=2 17%), and perception of personal health (n=1, 8%).

Prioritisation exercise

The most frequently prioritised outcomes ranked by patients were 'patient-reported confidence/empowerment related to reproductive decisions' (n=10, 67%), 'genetic counselling provided sufficient information to meet patient needs' (n=8, 53%), 'offering RGCS preconception is preferred (n=6, 40%), 'patient-reported anxiety' (n=5, 33%), and 'barriers and facilitators influencing patient experience of RGCS' (n=5, 33%).

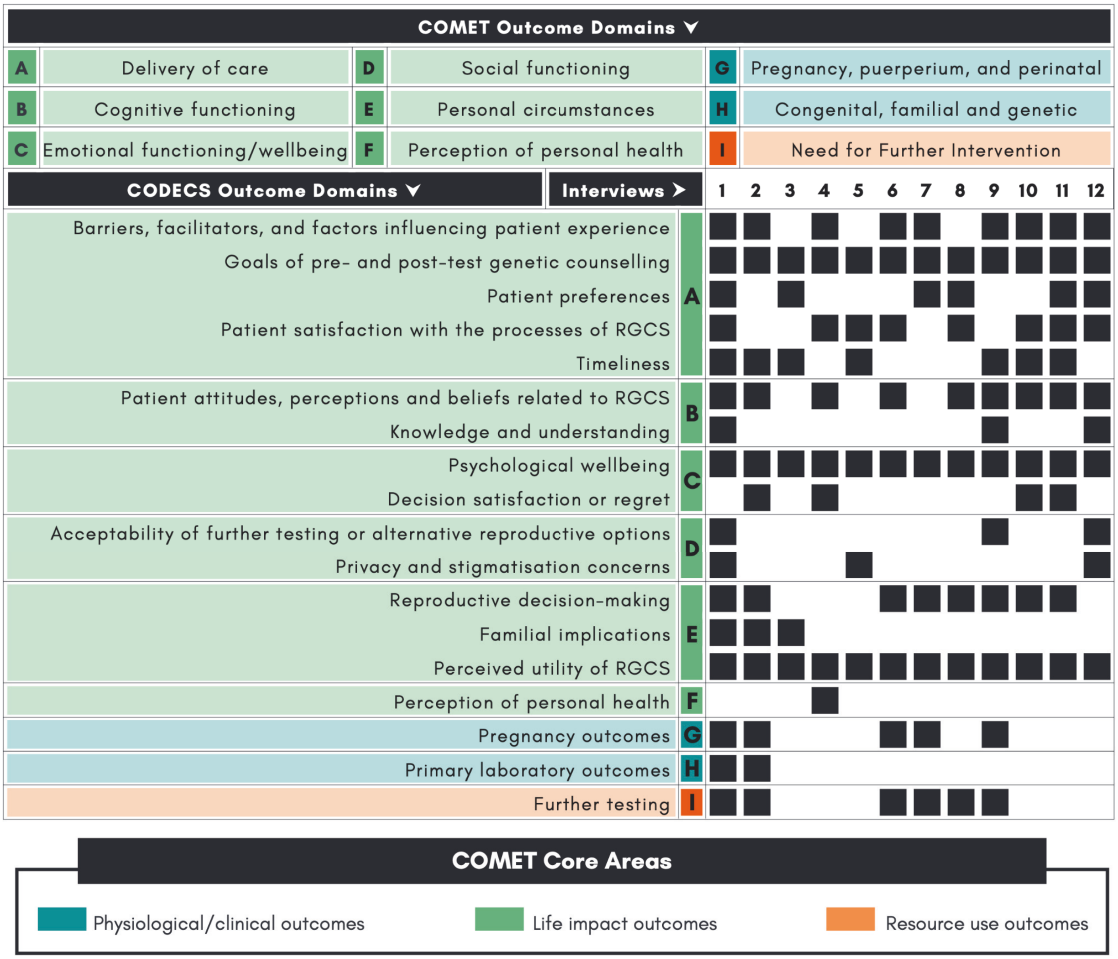

Figure 11: Block diagram illustrating the CODECS outcome domains represented across interviews

COMET core areas indicated by colour, COMET Outcome Domains indicated by A-I, CODECS Outcome Domains as listed in full.

5.7 Discussion

Patients are ideally placed to identify outcomes that capture their needs and experiences. In this qualitative study we sought to understand what outcomes are considered important to patients who undertake RGCS. The themes and outcomes we describe have implications for future research and for the development of a core outcome set that is inclusive of the patient perspective.

Participants highlighted informed choice and information needs as key areas for improvement in their pre- and post-test genetic counselling experience. When considering informed choice, it was clear that participants experienced routinisation of RGCS in certain settings. The concept of routinisation has been explored broadly in the prenatal literature, especially in non-invasive prenatal screening [23] and has also been highlighted

as an area of concern regarding the societal impact of RGCS [24,25]. Whilst there are many aspects and definitions of routinisation, most pertinent to these interviews was how healthcare providers frame RGCS. Healthcare providers often have the patient's trust and are assumed to know best, therefore when they present RGCS as routine there is potential to undermine the ability of the patient to make an informed choice about whether to accept screening [26]. This can lead to a lack of deliberation regarding the implications if found to be at increased risk [23].

Routinisation may also result in patients feeling pressured to accept RGCS, feeling disempowered in their decision-making, and may affect societal perceptions on the acceptability of declining RGCS or not intervening to prevent the birth of an affected child [27]. Considering that patient-centred care is a key goal of genetic counselling, addressing routinisation and how it may negatively impact the patient experience of RGCS needs further exploration. Whilst some literature has explored this topic, little experiential evidence is available to guide appropriate implementation of RGCS as it becomes increasingly available to the general population [24,28,29].

Information provision is an important component of informed choice, with a high degree of variability described by patients in this study. Participants discussed their perception of whether their information needs were met, areas where more information was needed, and disclosed how they were provided information ranging from verbal discussions, pamphlets, and online education. A recent publication documenting the development of a decision aid highlights many of the aspects of information provision that patients discussed in our interviews [30]. An ACMG practice resource provides recommendations on the information that should be provided during pre- and post-test genetic counselling and reflected both where information provision was good and where it was lacking for our participants [31]. These two examples of evidence-based resources to guide healthcare providers involved in genetic counselling for RGCS are valuable additions to the implementation of RGCS. The outcomes identified in this study, in concert with recent publications that document the key patient information components, set a strong foundation for future studies to accurately assess if patient information needs are being met and informed choice facilitated.

In our previous systematic review of quantitative studies[4], we highlighted the heterogeneity in psychological outcomes measured in studies on RGCS. There were a wide variety of psychological outcomes chosen by researchers, anxiety and worry being principle among these. However, no evidence exists for why these patient-reported

outcomes were chosen and if patients were consulted to inform the most meaningful outcomes to assess. In this qualitative study, as well as in a systematic review of previous qualitative studies on RGCS [5], we identified grief as a relevant psychological outcome in increased risk couples. The concept of grief as an emotional implication of genetic diseases has been explored across the genetics literature [32] and it has been identified as an important component of the adjustment period for increased risk couples following RGCS [33]. However to our knowledge, grief has not been incorporated into any quantitative evaluations of RGCS to date. In this study, grief was evident across increased risk couples and related to tangible losses such as the termination of affected pregnancies and fetal losses, as well as less tangible concepts such as the expected pregnancy journey, time, and adaptation to a medicalised process to a healthy child. Grief, bereavement and traumatic stress as a result of reproductive losses have been explored in obstetric and fertility settings that are innately intertwined with RGCS. Reproductive loss has been defined as "*any absence of innate function, missing of a promised child, or a tangible loss surrounding the natural human cycle of propagation*", and covers a wide range of losses [34]. Reproductive losses experienced by couples identified as increased risk through RGCS are broad and may include the experience of prenatal diagnosis leading to termination of an affected pregnancy, undertaking IVF/PGD with unsuccessful cycles or additional fertility challenges, loss of planned future children if results inform the decision to reduce planned family size, or loss of being biologically related to future children if they elect to use donor gametes; with RGCS being the inciting event that leads to the experience of these reproductive losses. As such, there is a need to investigate grief in the setting of RGCS to ensure that increased risk couples are supported in their journey to a healthy child.

The experience of complex grief is a potential adverse outcome of RGCS. While adverse outcomes are unlikely to be seen in the majority of patients undergoing RGCS, similar to other areas of genetics it is likely that a small percentage of patients will be affected and require additional supports. As the number of individuals from the general population accessing RGCS grows, even a small percentage may equate to a significant number of patients. Individuals with increased risk results are most likely to experience complex and ongoing psychological impacts following RGCS, and this group is significantly under-explored in the literature. Only 2 studies from our systematic review of quantitative studies [4] had measured psychological wellbeing in a cohort that included increased risk couples (combined sample size n=11). In comparison, five studies from our

systematic review of qualitative studies [5] included increased risk couples (combined sample size n=50). However, the concepts from such qualitative work are yet to be translated into measurable outcomes used in the evaluation of RGCS. Training in grief and loss is considered an important aspect of genetic counselling practice [35]. A recent study explored the role of genetic counsellors in mitigating complex or prolonged grief following termination of pregnancy for fetal anomalies, and identified a major role for genetic counsellors in facilitating adaptive coping [36]. Future research aiming to gain a better understanding of grief related to reproductive losses in the setting of RGCS will ensure that health providers can provide support and promote effective coping in increased risk couples. A clear understanding of the frequency and severity with which increased risk couples may experience complex grief is needed if we are to develop evidence-based practice recommendations based on the assumption of negligible harms.

We did not specifically seek to explore barriers in this study, but the prevalence with which participants raised barriers highlights that these are evident to patients undertaking RGCS and frequently impact their experience in negative ways. Participants identified three key areas; cost and accessibility, awareness amongst primary care providers and the community regarding RGCS in the preconception setting, and broad social factors that present both practical and psychological challenges for patients (e.g. entrenched societal views of termination and stigmatisation). A recent systematic review exploring barriers and enablers from the practitioner perspective captured many of the same barriers identified in this study, highlighting a need for further research informed by implementation science and behaviour change theory to address them [37]. Recent commentaries from Australia [24], the USA [38], and The Netherlands [39] all contribute to this growing recognition of the social context, barriers, and challenges that are key to consider in the implementation of RGCS. An important aspect of the barriers discussed by participants was timeliness. Cost and accessibility meant that many patients delayed or procrastinated about screening, and all participants that had accessed RGCS prenatally or following a fetal loss expressed regret that RGCS had not been accessible preconception. Those that had accessed termination of pregnancy perceived that a preconception offer could have spared them that experience and subsequent stigmatisation based on their reproductive decisions. A preference for patients to be offered RGCS preconception is prevalent across the literature on this topic [37,40], and will likely be a continued focus of research to address barriers and inform best practice as RGCS becomes widely implemented.

The concept of empowerment is recognised as a significant outcome of RGCS and is frequently framed as a primary goal [41-44]. This study provides valuable insight into what patients consider the primary goal of RGCS and their perceived utility of RGCS. Participants defined reproductive decisions made by couples accessing RGCS as an important outcome and reflected that RGCS provided the information needed to make such decisions. They further elaborated on a second outcome of empowerment to reflect how equipped couples felt to make these decisions. The outcome of reproductive empowerment was the most highly prioritised outcome from these interviews. McAllister et al. have established empowerment as a key outcome of clinical genetic services [45,46], work which subsequently informed the development of an empowerment scale for use across a range of genetic settings [47]. Lewis et al. expanded on this work and, similar to our findings, identified reproductive empowerment as the main outcome of RGCS [48]. Despite this existing work, no quantitative studies published to date have evaluated empowerment using a patient-reported outcome measure in a RGCS cohort. Instead informed decision-making underlies the concept of empowerment in current literature, with an assumption that RGCS empowers patients by providing information that they can use to make reproductive decisions in line with their estimated chance of having an affected child and their values regarding this. There are some issues with this approach though. Informed choice has been evaluated predominantly regarding uptake, with studies aiming to determine whether patients make informed decisions to access RGCS. The multi-dimensional measure of informed choice (MMIC) is most often used, assessing patient knowledge, attitude to testing, and whether behaviour (i.e. the choice to accept or decline testing) is in line with their knowledge level and attitude [49]. This pre-test approach ensures appropriate access to RGCS, but does not capture informed decision-making following results. Post-test evaluations aimed at capturing empowerment often assess intended and actual reproductive decisions made by prospective parents based on RGCS results. These current pre- and post-test approaches ground their conceptualisation of empowerment in information and behaviour, but these are only two aspects of a more complex construct. McAllister et al. define empowerment as a construct that encapsulates five concepts: (1) Decisional control – being able to make important life decisions in informed ways (2) Cognitive control – having sufficient information about the condition, including risks to oneself and one's relatives, and any treatment, prevention and support available (3) Behavioural control – being able to make effective use of the health and social care systems for the benefit of the whole family (4)

Emotional regulation - being able to manage one's feelings about having a genetic condition in the family and (5) Hope - being able to look to the future with hope for a fulfilling family life, for oneself, one's family, and/or one's future descendants [47]. The latter two components, emotional regulation and hope, are of particular relevance to this study. Participants described empowerment as a long-term or overarching outcome of RGCS, having ongoing relevance far beyond the immediate post-test period. Learning to cope with the implications of their results, manage their psychological wellbeing over time, and have hope that they are working towards a healthy pregnancy underlined participant discussions around empowerment. While some aspects of empowerment have been captured in the literature to date through a focus on informed choice and reproductive decisions made by increased risk couples, there is nuance that is lost without considering the other aspects that make up the construct of empowerment. We have also previously highlighted timeliness as a component of patients perceived utility of RGCS [5]. Similarly, participants in this study preferred preconception offers as a way to further bolster empowerment. There is currently no consensus definition of the utility of RGCS, hence there is an opportunity to incorporate the concepts we have identified in future studies. The clear conceptualisation of utility encompassing both the clinical aspect of reproductive decisions and the personal aspect of empowerment will ensure a truly patient-informed and ethically-oriented definition of utility for the purpose of a core outcome set.

This study was informed by evidence from previous COS development studies that showed the valuable contribution of patients to the outcomes identified [8,50]. Consistent with these, we identified eighteen outcomes that were unique to patient interviews and would not have been identified from a systematic review alone. We also gained detailed and nuanced insight into how patients conceptualise outcomes of their RGCS experience, which highlighted clear gaps in current evidence and can inform future research. We report a novel methodology for eliciting outcomes from patients that facilitated this rich depth of understanding. This study supports current evidence on the importance of incorporating patient stakeholder consultations in a COS development study to ensure that outcomes are meaningful to patients, and perhaps more significantly, why these outcomes are important.

5.8 Conclusion

In consultation with patient stakeholders, we elicited a detailed understanding of outcomes considered important to patients undertaking RGCS. Grief and empowerment were highly valued outcomes that have not been assessed in studies of RGCS to date. Patients experienced barriers and challenges related to the societal context in which RGCS occurs, and experienced negative repercussions of routinisation that compromised informed choice. This study highlights that patients can be active partners in identifying meaningful outcomes of a health intervention, and identify outcomes that may not be have been considered without their input. To achieve patient-centred and ethical implementation of RGCS there must be uptake of outcomes that matter to patients in future research.

5.9 Limitations

Participants responded to a broadly distributed EOI, therefore there is a chance of selection bias. In addition, many of our participants had experienced fetal loss and we acknowledge that psychological outcomes may be overrepresented. The majority of participants were female, with 3 male partners participating in a couple interview. This may reflect upon recognised differences in the role of reproductive partners in decision-making regarding family planning and pregnancy. There is a chance that different outcomes may be considered important by male reproductive partners. As the purpose of these interviews was to elicit as many outcomes of potential significance as possible, any bias in participants may be beneficial in identifying outcomes that are not evident in other samples. Any overrepresentation will also be mitigated in subsequent consensus steps of the CODECS study, as the frequency with which outcomes have been seen does not influence whether they are presented to stakeholders for consideration for inclusion in the COS. In aiming for a diverse sample we achieved some degree of representation across different ethnic groups; however, all participants were from developed, English-speaking countries and were highly educated. Further work is needed to ensure that outcomes included in a COS are generalisable and representative of the needs across all populations accessing RGCS.

5.10 Research team

ER (female) is a PhD candidate and associate genetic counsellor with training in qualitative research methodology, who at the time of data collection had 7 year's experience discussing genetic health conditions and genetic testing with patients across clinical, research and laboratory settings. Participants were aware of the professional background of the interviewer. CJ (female) is a senior lecturer in the genetic counselling program at the University of Technology Sydney (UTS), registered genetic counsellor and registered nurse with qualitative research experience. AM (female) is an associate professor in genetic counselling at UTS, led the establishment of the Master of Genetic Counselling program at UTS, and is a registered genetic counsellor with qualitative research experience. TN (male) is a professor of psychology at UTS, and an endorsed clinical psychologist with qualitative research experience. AC (female) is a PhD candidate and certified genetic counsellor with training in qualitative research methodology.

5.11 Additional supporting information

This section contains additional information pertinent to the conduct of this qualitative study that was not feasible to include within the published manuscript. Described below is the theoretical underpinning for this qualitative study, including a reflexive statement.

5.11.1 Theoretical underpinning of the study design

Ontology, epistemology, and the research paradigm

Research is inherently based in philosophical beliefs about knowledge, which shape and influence the goals, conduct and outcomes of research. This study is guided by the ontological belief of relativism, which posits that there are multiple versions of reality, shaped by the context and perspective of those that are experiencing it.[51] An emic epistemological perspective is adopted, placing the researcher within the context in which research is being conducted, recognising the subjective nature of research and accounting for the influence and perspective of the researcher on the research.[52] This is distinct from an etic perspective, which would place the researcher outside of the research and aim at all times to maximise objectivity and remove the influence of the researcher as much as possible. Combined, the guiding principles of the relativist ontology and emic epistemology inform a constructivist/interpretivist research paradigm that theoretically underpins the methodology and methods that were chosen in this study.

This paradigm fundamentally values participants' views and opinions, and recognises that these are situated within their individual experience of reality as shaped by their social context.[53]

Methodology and methods

Whilst there is not one definition of methodology, most definitions agree that it refers broadly to the philosophy that guides how data should be collected, and is informed by the research paradigm.[53] Methods on the other hand are the data collection and analysis tools or techniques that make up the practical aspects of the research process.[51]

Based on the previously described research paradigm, our methodological choices were informed by the goal of understanding patient experience of RGCS from the individual perspective of those who have undertaken it. In order to understand outcomes that are important to patients, we adopted the methodology of phenomenology, the foundation of which lies in the attempt to describe and understand a phenomenon as experienced through the perspective of those with lived experience of it.[54] Whilst interpretations of phenomenology and it's applicability in medical research are broad, on a basic level it focuses on the need to speak to patients directly and engage with them meaningfully in order to understand their unique perspectives. This philosophical underpinning guided the use of semi-structured interviews and reflexive thematic analysis as our methods.

Design coherence

When taken together we hope there is now a clear understanding of the positioning of the researcher in this study. The ontological and epistemological views described together inform the research paradigm, which in turn provides a rationale or basis for the methodology and methods that were chosen. In a cyclical manner, the methodology and methods reflect the research paradigm and a clear representation of each of these aspects is what defines design coherence (Figure 12).

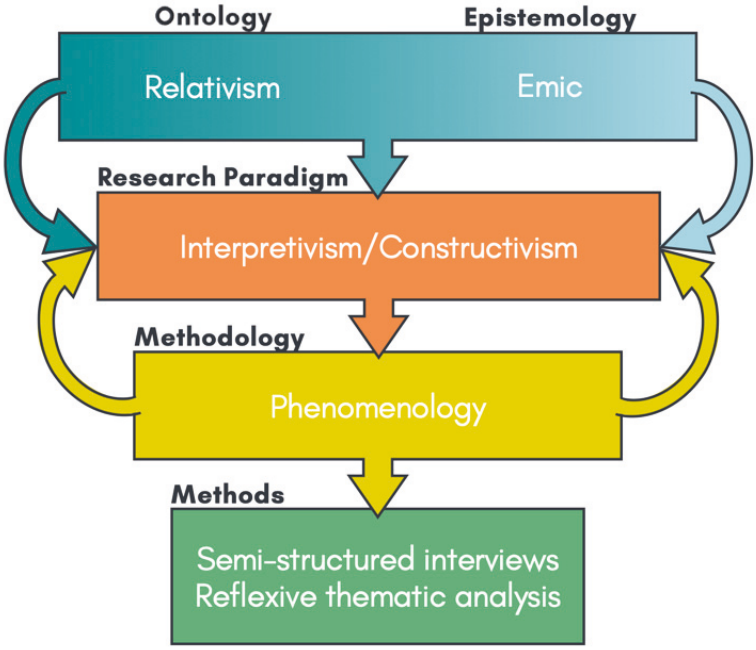

Figure 12: Positioning of the researcher
Ontology, epistemology, research paradigm, methodology and methods

5.11.2 Statement of reflexivity

Reflexivity is the open acknowledgement of the influence the researcher, the research team, the topic, and the subjects may have on the findings, and the deliberate attempt to address and transparently report such influences.[55] Reflexivity involves reflection on the positioning of the researcher as well as awareness of the wider social setting pertinent to the research topic.[56] Gender, ethnicity, and professional status are explicit factors that can influence how participants perceive the interviewer and therefore how they answer questions.[57,58]

Influence of the researcher

As the primary interviewer, I brought to these interviews both implicit and explicit influences on the research. I identify as female and am from a White ethnic background. I am a genetic counsellor by profession and participants were aware of my professional status. These were explicit characteristics able to be observed or known by participants. I shared many of these explicit characteristics, including gender and ethnicity, with the majority of participants. This may have facilitated an initial level of rapport with participants and enhanced their comfort to discuss sensitive topics. On the other hand, for the participants that did not share these characteristics there is a chance that they

could have negatively influenced data collection. While no overt influence was noted in the data, nor in the reflexive notes I wrote after each interview, there is a chance that different data would have been elicited from patients if they were matched by gender or ethnicity to another interviewer. There is conflicting evidence in the literature regarding the influence of such explicit characteristics, but this is a consideration for future research that seeks to expand the generalisability of this study to wider populations.[57,58]

I also brought implicit views and values to the research. My role as a genetic counsellor with experience offering RGCS in the prenatal and preconception settings shapes my views in support of the offer of RGCS to all women planning a pregnancy or in their first trimester, consistent with current practice recommendations. My practical experience and in-depth knowledge of current research evidence on RGCS inform a world view that values RGCS but recognises the necessity for increased standardisation and higher quality evidence to demonstrate this value. My ethical values focus on equality and accessibility of RGCS and drive a desire to contribute to research that can rectify current imbalances in equitable access. I also have an insider perspective to this study, having personal experience of undertaking RGCS. This status as an insider was not disclosed to participants, however, the ability to relate to participants may have influenced interview style and facilitated the high level of rapport that was needed to engage in a collaborative process with participants.

Due to my immersion in the literature prior to conducting these interviews, I brought extensive knowledge of the landscape of outcomes assessed on this topic. Throughout the interviewing process, I wrote a reflection following each interview to consider what was discussed, initial impressions of the themes of the interview, and any aspects that I felt I may have overtly influenced. In two early interviews, I reflected that I perceived the potential for participants to be led by me during the co-design stages of the interview. I discussed this reflection with my primary supervisor (CJ) and based on her expertise as a practiced qualitative researcher, CJ provided advice regarding re-phrasing certain prompts to minimise leading in subsequent interviews.

Influence of participants

Throughout the course of conducting this study I reflected on the influence that the participants as an overall cohort may exert on the data collection and interpretation of results. A significant proportion of participants had experienced a fetal loss prior to undertaking RGCS, which may have influenced an over-representation of psychological

outcomes in the dataset. I reflected on this during the interview and analysis process and discussed it with my supervisory team. To minimise any overt skewing of the data, during coding of the interviews only excerpts directly related to RGCS were extracted and those related to broader discussions of the impact of the loss were not coded for the purpose of this study.

I also observed that the majority of participants expressed positive views of RGCS, and as this was a self-selected group recruited through a social media approach it is possible that those with less positive views were not captured. I reflected on this when developing the study themes, and in defining each outcome I was careful to consider both positive and negative interpretations of each outcome. For example, if the outcome 'satisfaction with a health care provider' was elicited from the patient, the measurement of this outcome in practice would allow a patient to report either satisfaction or dissatisfaction on a scale.

Influence of the social context

There are currently limited opportunities to access RGCS and issues with equitable access due to high costs. Most patients that access RGCS are of high socioeconomic status, highly educated, and outside of increased risk groups are overtly from White ethnic backgrounds. These characteristics were evident in the cohort recruited for this study as well, therefore it was pertinent to recognise that this broader context may influence what outcomes are considered important to these patients and may not be the same outcomes that are important to a more diverse population.

5.12 Summary of supporting data available in Appendix C

The following supporting data are available in Appendix C:

Supplementary material C.1 – Guidance informed study design

Supplementary material C.2 – Social media expressions of interest

Supplementary material C.3 – Eligibility and demographic survey

Supplementary material C.4 – Emails to respondents/participants

Supplementary material C.5 – Participant information sheet

Supplementary material C.6 – COMET/CODECS taxonomy version 1.2

Supplementary material C.7 – Interview schedule

Supplementary material C.8 – Example virtual whiteboard

Supplementary material C.9 – Methodological feedback from participants

5.13 References

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Chapter 6: Consensus process

6.1 Chapter overview

In this chapter, I present the consensus process undertaken with Australian and New Zealand (AUS/NZ) stakeholders. The details of a planned international Delphi process are given in Chapter 2. Electing to conduct an AUS/NZ only survey meant that several changes to the planned protocol were needed. These are outlined in full in Appendix D.

This chapter is structured per a published pre-print that is under consideration at the *European Journal of Human Genetics*.

> Richardson E, McEwen A, Newton-John T, Crook A, Jacobs C. Defining core outcomes of reproductive genetic carrier screening: A Delphi survey of Australian and New Zealand stakeholders. 2022. Pre-print submitted to *In Review*.

6.2 Abstract

Understanding the benefits of health interventions is needed to inform best practice and ensure responsible implementation of new approaches to patient care. The assessment of outcomes is an important part of demonstrating these benefits. There is no current consensus about which outcomes are appropriate for the evaluation of genetic health interventions, including genetic testing and genetic counselling. The Core Outcome DEvelopment for Carrier Screening study has addressed this lack of guidance by undertaking a systematic approach to understanding the outcomes that can meaningfully capture the benefits of reproductive genetic carrier screening (RGCS). Herein, we report on a consensus process to determine the degree of consensus among Australian and New Zealand stakeholders regarding the core outcomes of RGCS. An iterative, two-round online Delphi survey was conducted. Panellists consisting of patient participants and genetic health professional (GHP) participants (n=12) ranked 83 outcomes according to their perceived importance on a nine-point Likert scale. Using the distribution of rankings, outcomes were grouped into tiers representative of their perceived level of importance and agreement between groups. The top tier outcomes were agreed to be critically important for all future studies and were used to define a preliminary core outcome set encompassing the domains (1) primary laboratory outcomes, (2) pregnancy outcomes, (3) resource use and (4) perceived utility of RGCS. These findings will help to guide the selection of meaningful

outcomes in studies aiming to evaluate the value of RGCS. A future international consensus process will expand on these findings and guide the inclusion of diverse perspectives across the range of settings in which RGCS is offered.

6.3 Introduction

Demonstration of the benefits of genetic health interventions, including genetic counselling and genetic testing, is needed to inform best practice, guide policy and funding, and ensure responsible implementation in patient care. The assessment of outcomes that can accurately capture the impact is an important component of demonstrating these benefits.[1,2] A range of outcomes have been reported across the literature, but there is limited evidence to identify which outcomes are the most appropriate to assess. Recent systematic approaches have attempted to understand the outcomes of genetic counselling[3-6] and genetic services[7,8] at a broad scale. However, applying this knowledge to the evaluation of a specific genetic health intervention remains challenging. This study focused on the outcomes of reproductive genetic carrier screening (RGCS) as a model for how a systematic process of defining and prioritising outcomes on a specific topic, known as a core outcome development study, can lead to clarification of outcomes of importance and guide future research.

RGCS identifies individuals and couples with an increased risk of having a child affected by a recessive or X-linked condition. Prospective parents can use this information to inform their reproductive decision-making. RGCS has been offered since the 1970s in groups with a high prevalence of specific genetic conditions, such as Tay-Sachs disease in Ashkenazi Jewish communities and thalassaemia in communities of Mediterranean descent.[9-11] Practice recommendations initially endorsed the targeted offer of RGCS in such populations with prior indications. However, with the expansion of genomic testing capabilities and increasing recognition of the limitations of ethnicity-based risk estimation, professional organisations now support the offer of RGCS to all women planning a pregnancy or in their first trimester.[12-14]

As RGCS moves from a targeted offer in increased risk groups, to a population-based screening program available broadly to the general population, an understanding of the benefits and potential harms is crucial to ensuring responsible implementation.[15] The Core Outcome DEvelopment for Carrier Screening (CODECS) study aims to define a set of core outcomes that have been identified through a rigorous review of current knowledge and in consultation with key stakeholders.[16] The goal of a core outcome set (COS) is to

ensure that outcomes being assessed in research can meaningfully capture the impact of RGCS, which will increase the likelihood that they can directly inform practice and policy.[16] In a systematic review of quantitative studies reporting RGCS we identified a high degree of outcome heterogeneity, which illustrated the difficulty identifying which outcomes are most informative and appropriate to assess in studies of RGCS.[17] We also found that few studies have incorporated patient-reported outcome measures and no evidence of patient involvement in deciding which outcomes are relevant, which has led to a limited representation of the patient perspective. A sequential review of the qualitative literature highlighted the important patient-led outcomes that have not been incorporated into quantitative evaluations of RGCS to date and identified gaps in knowledge about the benefits and potential adverse impacts.[18] Consultations with patient stakeholders further re-iterated the importance of these patient-led outcomes as a focus for future research.[19]

A consensus process through which all collated outcomes from previous steps are reviewed, refined and prioritised by key stakeholders is the culmination of a core outcome development study. The goal of this process is to determine which outcomes are the most important to define as core outcomes that should be reported in all future studies on RGCS. This consensus process typically includes a Delphi survey and consensus meeting that includes all relevant groups and stakeholders that would be impacted by the definition of a core outcome set. Herein, we report a Delphi survey of Australian and New Zealand (AUS/NZ) stakeholders as a first step in a consensus process to define a COS for RGCS. The aim of this Delphi survey was to determine the degree of consensus among AUS/NZ stakeholders on the core outcomes of RGCS and to identify any further outcomes for inclusion in future steps of the consensus process.

6.4 Materials and methods

6.4.1 Study design

The Delphi process is a validated method for achieving consensus across a range of settings. In studies aiming to develop a COS, the Delphi process is used to refine and prioritise the 'long list' of outcomes collected from previous steps, such as systematic reviews and stakeholder consultations.[20] We designed an iterative online two-round Delphi survey to be completed by participants with experience with or expertise in RGCS. This study is reported per recommendations from the Core Outcome Measures in Effectiveness Trials (COMET) initiative.[21] Ethics approval was granted by the University of Technology Sydney Ethics Committee (UTS HREC ETH20-5179).

6.4.2 Participant selection

An expert panel of AUS/NZ participants was convened. Participants belonged to two groups: patients who had undertaken RGCS and health professionals with roles encompassing offering RGCS as part of a clinical service conducting research on RGCS or contributing to policy and practice recommendations. Participants were selected purposively based on their experience of RGCS across AUS/NZ. Patient participants were identified from previous stakeholder consultations in which co-design methods were used to elicit outcomes of importance to patients and had provided consent to be approached for the Delphi survey.[19] Health professional participants were identified by the first and last authors of publications included in our sequential systematic review[17,18], listed committee members from key policy and practice recommendations, and through professional networks within AUS/NZ.

Sample size

Guidance about what constitutes a sufficient number of Delphi survey participants is not currently available, and there is wide variability in panel sizes across core outcome development studies.[22,23] Smaller panels have been shown to produce reliable results when composed of experts with similar experiences who are immersed in the research topic. Therefore, the goal was to convene a panel of 12 experts with a common experience and understanding of RGCS as currently offered in AUS/NZ.[22,24]

Recruitment

All participants were approached via email, provided with brief information about the purpose of the Delphi survey and prompted to respond to the invitation if they were interested in participating (available in Appendix D). Health professionals were asked to suggest alternative participants if they were unable to participate themselves. The survey was anonymised and participants were unaware of the identity of other participants. Invitees were informed that participation was voluntary and would involve completing 2-3 surveys over a 6-month period, each expected to take about 30 minutes. The importance of committing to the full consensus process was conveyed to invitees.

Prior knowledge

Four patient participants had previously participated in stakeholder consultations using co-design methods to elicit outcomes of importance to patients undertaking RGCS, one was not eligible for the stakeholder consultations as they had not received their RGCS results at the time of recruitment but had expressed interest in participating in the Delphi survey once eligible, and one was a patient representative involved in the CODECS study advisory group. Patient participants were therefore familiar with the concept of outcomes and were able to recall the outcomes discussed during their previous interactions with this study. All health professional participants were actively involved in practice, research and/or policy on RGCS and may have been aware of previously published work, including a systematic review[17,18] that had been published at the time of the Delphi survey.

6.4.3 Compiling outcomes

All outcomes collected from the systematic review process[17,18] and qualitative interviews with patient stakeholders[19] were collated into a block diagram. The combined list comprised 175 outcomes across 25 CODECS outcome domains. Each outcome domain was reviewed by ER and the Study Management Group (SMG: CJ, AM, TNJ) to determine which outcomes warranted inclusion in the Delphi process. Exclusion from the Delphi process was based on the relevance to the scope of the COS. Outcomes that were highly specific to a particular group or not widely applicable to pan-ethnic carrier screening in a population-based context were considered for exclusion. Similar or overlapping outcomes were combined where appropriate. Following review, 83 outcomes across 21 domains were included in Round 1 (Figure 13).

6.4.4 Piloting Delphi questions

The survey was piloted with two patient representatives and two health professional representatives. Participants were asked to comment on the phrasing of each outcome, clarity of the instructions, and the appropriateness of the questions for both patient and health professionals. Each question was structured according to the overarching outcome domain, meaning that Round 1 consisted of 21 questions, with multiple outcomes to rate within each. Comments provided during piloting were used to make minor changes to the wording before the outcomes were finalised.

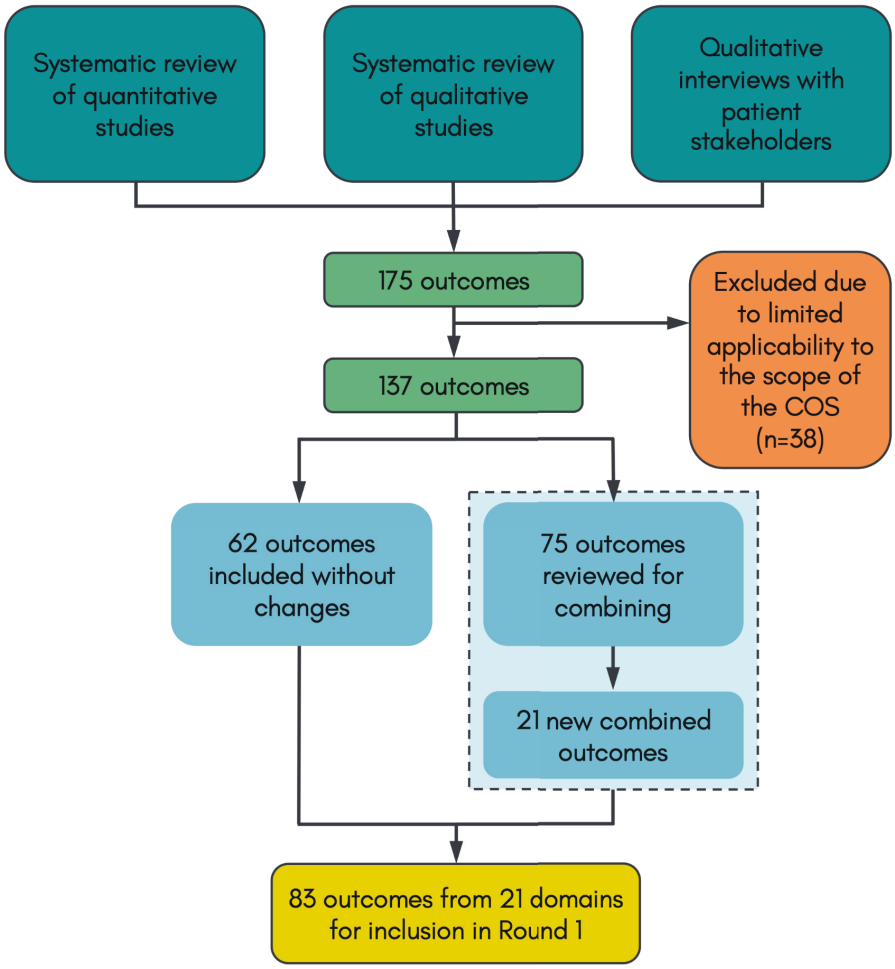


Figure 13: Compiling outcomes for inclusion in Round 1

6.4.5 Data collection

Data were collected using the Qualtrics platform.[25] The complete survey is available in Appendix D. Participants were sent reminders when 2 weeks, 1 week and 1 day were remaining to complete the survey for both rounds.

Round 1

The Round 1 survey was available to participants for 4 weeks (Jan-Feb 2022). Participants rated the importance of 83 outcomes using a nine-point Likert scale. Rankings 1-3 indicated "limited importance", 4-6 indicated "important but not critical" and 7-9 indicated "critical importance", in accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process.[26] A free text box was provided for participants to suggest new outcomes, and separate free text boxes were available for participants to record their general comments about each outcome. Distributions of Round

1 rankings were plotted graphically and reviewed with a statistician to determine the appropriate thresholds for inclusion in Round 2, as reported below.

Round 2

Round 2 was opened 3 weeks after Round 1 closed and was available to participants for 6 weeks (March-April 2022). Participants were shown their own rankings from Round 1 for each outcome, and the mean, median and range of rankings per group. Instructions on how to approach the re-ranking of outcomes and clarifications of certain outcomes were provided. De-identified comments from Round 1 were shown where relevant. Participants were asked to re-rank items on the same nine-point Likert scale. Distributions of Round 2 rankings were plotted graphically and grouped by the degree of consensus regarding the importance of each outcome. The SMG discussed the results following Round 2 and determined that a third round was unlikely to provide additional insights and would be overly onerous on participants; therefore, the Round 2 rankings were used to establish tiers of consensus to inform a preliminary COS.

6.4.6 Data analysis

Defining thresholds for inclusion/exclusion

A range of consensus definitions are used across the Delphi literature.[23] Previously defined thresholds from our published protocol[16] were not applicable because of significant differences in the sample sizes between the planned international Delphi survey and this smaller survey of AUS/NZ stakeholders. Changes to these thresholds are discussed in Appendix D. When determining an alternative appropriate threshold for use in this Delphi survey, we elected to apply the approach defined by the Standardised Outcomes in Nephrology (SONG) initiative, which uses the mean and median ratings of each outcome in context with the overall distribution of rankings to determine appropriate cut-offs for inclusion or exclusion in subsequent rounds.[27] This approach suggested a baseline threshold for inclusion in Round 2 if the outcome had a mean and median of >7, with the caveat that this threshold may need to be adjusted depending on the distribution of rankings.

At the conclusion of Round 1, the distribution of rankings was analysed by ER and reviewed by a statistician to determine the appropriate thresholds for inclusion in Round 2. Outcomes with a mean ≥6.5 and median ≥7 from either participant group and ≥4 in the other group were included in Round 2. Setting the mean threshold at 6.5 was a pragmatic

decision based on the appropriateness of decimal values when calculating the mean, as opposed to the median which was restricted to absolute numbers based on the nine-point Likert scale used. The mean, median and proportion of participants who rated each outcome 7-9 (critically important) were calculated separately for patients and health professionals. Outcome decisions (include/exclude) and any changes to the proposed outcomes for Round 2 were reviewed with the SMG for approval. The sample size was too small to conduct subgroup analysis to identify statistical differences between groups.

Defining consensus on the critical importance of outcomes

Consensus on outcomes considered to be of critical importance was defined as outcomes with mean and median rankings ≥8 in either group and a percentage of stakeholders rating the outcome as 'critically important' >70%. Any outcomes that reached this threshold in Round 1 were considered to have reached consensus regarding their critical importance and were not included in Round 2.

Changes to outcomes following Round 1

Based on participant feedback in Round 1, some outcomes were reviewed for re-wording or to be combined into new outcomes. ER prepared all outcomes that reached the threshold for inclusion in Round 2 and presented these to the SMG for agreement.

Quantitative analysis

The mean, median and proportion of participants who rated the outcome as critically important (7 to 9) were calculated for each outcome in both rounds. Data were analysed for patient and health professional groups separately. The overall distribution of rankings from both groups was plotted graphically. Outcomes with similar rankings were grouped into tiers representing the degree of consensus and importance attributed to each outcome. Outcomes that reached consensus as being critically important were used to define a preliminary core outcome following Round 2.

6.5 Results

6.5.1 Participant characteristics

A summary of the participants is provided in Table 7. Round 1 was completed by all 12 participants, seven from Australia and five from New Zealand. Equal representation was obtained between patient and health professional groups. Four patient participants had low risk results from RGCS (two individuals and one reproductive couple), one was identified as a carrier following a fetal loss due to an X-linked condition and undertook RGCS to exclude other genetic conditions, and one was part of a carrier couple identified through preconception screening. Health professional participants included genetic counsellors, clinical geneticists, researchers, policy-makers and genetic pathologists; the expertise of many health professional participants overlapped between multiple areas. Round 2 was completed by 10 participants (retention 83%).

Table 7: Characteristics of Delphi survey participants

Descriptor	Number of Participants
Gender (n=12)	
Female	10 (83%)
Male	2 (17%)
Country (n=12)	
Australia (AUS)	7 (58%)
New Zealand (NZ)	5 (42%)
Areas of expertise (n=18*)	
Patient who has accessed RGCS	7 (39%)
Genetic health professional (genetic counsellor or clinical geneticist)	5 (28%)
Researcher currently or previously involved in research on RGCS	3 (17%)
Policy-maker	2 (11%)
Genetic pathologist	1 (0.6%)

*Some participants had multiple areas of expertise

6.5.2 Distribution of rankings from Round 1 and inclusion in Round 2

The outcomes included and excluded from Round 2 are summarised in Figure 14. The mean and median rankings per group for each outcome are shown in Table 8.

Only one outcome reached consensus as being critically important to include in all future studies of RGCS after Round 1: *"Reproductive decisions made by patients post-test and long term"*.

Thirty-six outcomes were agreed as not being critically important to include in a COS, as indicated by mean and median scores below the defined thresholds in both groups and were excluded from Round 2. The remaining 46 outcomes and associated comments from participants were reviewed by ER. Twenty-two of the eligible outcomes were combined and re-worded into eight new outcomes for Round 2. No new outcomes were suggested by participants. The full outcome details are available in Appendix D. The distributions of rankings for each outcome are shown in Figure 15.

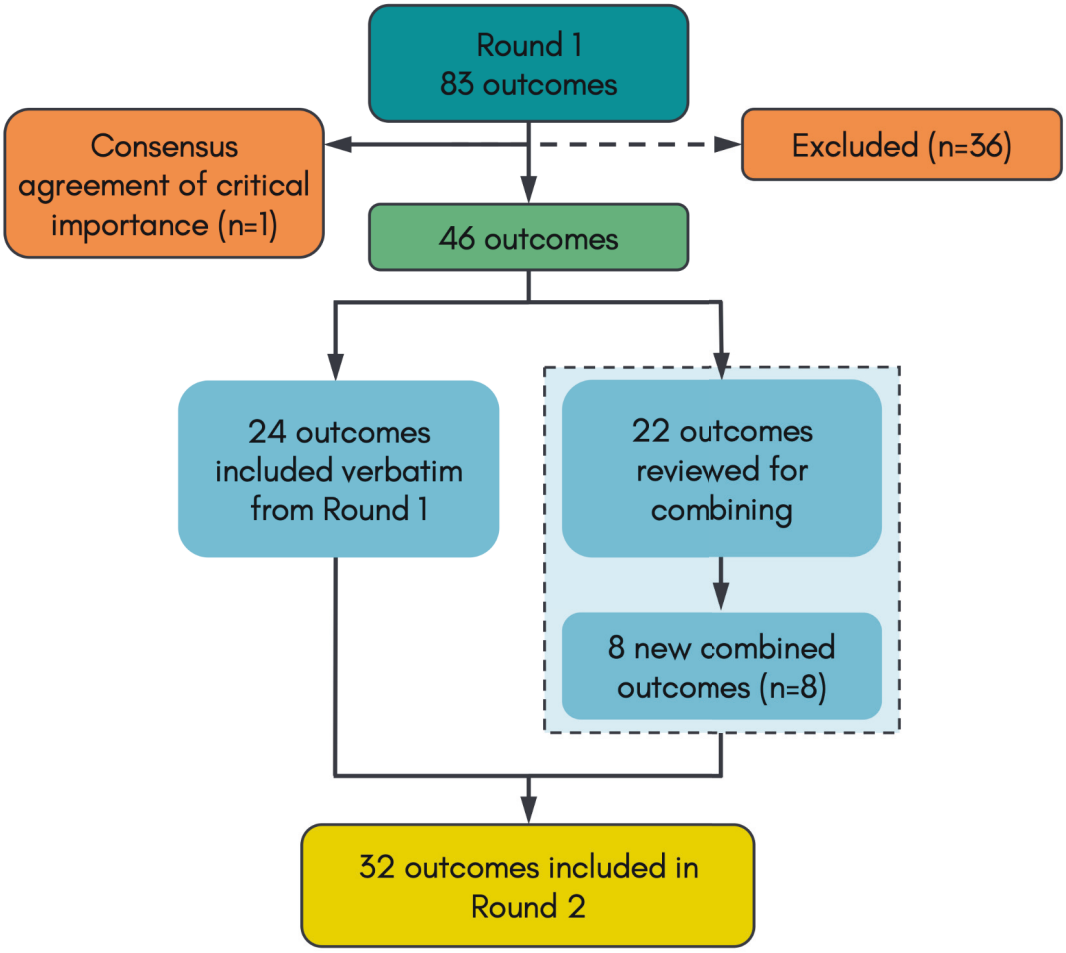


Figure 14: Reduction in outcomes based on Round 1 results

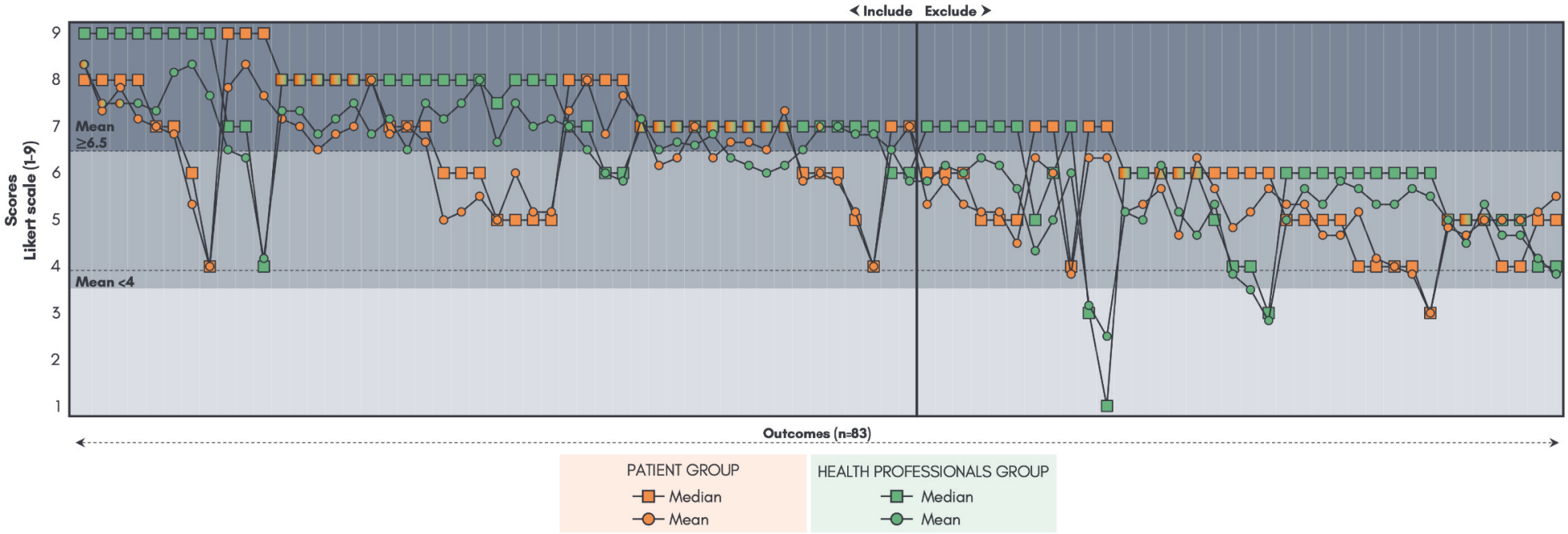


Figure 15: Distribution of rankings from Round 1

Vertical columns show the mean and median for each of the 83 outcomes; values for the patient group are indicated in orange and health professional group in green. Mean thresholds are shown to assist with interpretation. Per the defined criteria, outcomes with a mean ≥ 6.5 and median ≥7 from either participant group and ≥4 in the other group were included in Round 2.

Table 8: Round 1 rankings

CODECS Outcome Domains and Outcome Descriptions	Patients		Health Professionals	
	Mean	Median	Mean	Median
Domain 1 - Primary laboratory outcomes				
Carrier detection rate[a]	7.0	7	6.6	7
Identification of increased risk couples	5.3	6	8.3	9
Domain 2 - Secondary and incidental laboratory outcomes				
Identification of results that indicate the prospective parent undertaking RGCS is at increased risk of or affected by one of the conditions screened	6.8	8	7.2	8
Identification of variants where the association with disease risk is unclear	6.3	7	3.2	3
Domain 3 - Technical laboratory outcomes				
Laboratory errors leading to the incorrect interpretation of results	7.7	8	5.8	6
Test failure and requests for replacement samples	6.7	7	6.3	7
Domain 4 - Uptake of services				
Number of RGCS tests conducted	7.0	8	7.5	8
Uptake of RGCS	6.2	7	6.5	7
Decline of RGCS	5.2	4	5.7	6
Barriers and facilitators to access and uptake of RGCS	6.5	8	6.8	8
Domain 5 - Genetic counselling resource use				
Uptake of pre-test genetic counselling[a]	4.0	4	5.3	6
Time required for pre-test genetic counselling	4.2	4	5.3	6
Uptake of post-test genetic counselling for increased risk couples[a]	5.5	6	8.0	8
Mode of genetic counselling (e.g. face-to-face, telehealth)	3.8	4	5.7	6
Domain 6 - Further testing and reproductive decision-making				
Uptake of partner testing[a]	7.0	8	7.3	8
Barriers and facilitators to access and uptake of partner testing[a]	7.2	8	7.3	8

Uptake of prenatal diagnosis[b]	6.8	7	8.2	9
Barriers and facilitators to access and uptake of prenatal diagnosis	7.3	8	7.5	9
Reproductive decisions following an increased risk result	8.3	8	8.3	9
Barriers and facilitators of patient uptake of IVF/PGD in increased risk couples	7.8	8	7.5	9
Barriers and facilitators influencing patient experience of PND, IVF/PGD and TOP	7.2	8	7.5	9
Support needs when making reproductive decisions	6.0	5	7.5	8
Domain 7 - Pregnancy outcomes				
Results of PND (CVS or amniocentesis)[b]	7.3	8	7.0	7
Rate of fetal loss following PND[b]	7.7	9	4.2	4
Decision to continue or terminate a pregnancy identified as affected through PND[b]	8.0	8	6.8	8
Birth rates for conditions that were included in screening	8.3	9	6.3	7
Results of IVF/PGD utilised by increased risk couples	7.8	9	6.5	7
Domain 8 - Non-reproductive decision-making				
Lifestyle changes influenced by results of RGCS	6.3	7	2.5	1
Insurance decisions influenced by results of RGCS	5.7	6	2.8	3
Domain 9 - Timeliness				
Turnaround time for results	4.7	5	5.8	6
Gestational age in the prenatal setting[b]	5.7	6	6.2	6
Proportion of RGCS conducted within an ideal time-frame[b]	5.3	6	6.0	7
Time intervals between key steps of the RGCS process	5.0	5	5.3	5
Domain 10 - Patient attitudes, perceptions and beliefs related to RGCS				
Perceived chance of carrier finding and preparedness for an increased risk result	4.8	5	5.0	5

Patient attitude towards RGCS (at the time of the screening offer)	5.2	6	5.2	6
Patient attitude towards RGCS (after results)	5.3	6	5.0	6
Patient perception that RGCS will inform their reproductive decisions (at the time of the screening offer)	7.2	7	7.2	7
Domain 11 - Deliberation and informed choice				
Time spend on deliberating on the decision to accept or decline screening	3.0	3	5.5	6
Patient perception that they had sufficient information to make a decision to accept or decline screening	4.0	4	7.7	9
Patient perception that they were engaged in the decision-making process	5.0	6	7.2	8
Patient perception that they made an informed choice to accept or decline RGCS	5.2	6	7.5	8
Informed choice defined by congruence of knowledge, attitudes, and decision-making	5.3	6	5.8	7
Domain 12 - Goals of pre- and post-test genetic counselling				
Genetic counselling presents screening and further testing as a choice	5.2	5	6.8	7
Genetic counselling provides sufficient information to meet patient needs	5.2	5	7.0	8
Patient perception of the timing and method of information provision during genetic counselling	5.2	5	6.2	7
Genetic counselling supports informed decision-making	5.0	5	6.7	8
Genetic counselling provider was knowledgeable and empathetic	5.2	5	6.3	7
Genetic counselling was accessible	7.0	7	7.3	9
Genetic counselling promoted reproductive empowerment	7.0	7	6.5	8
Domain 13 - Knowledge and understanding				
Patient understanding of RGCS	5.8	6	6.5	7
Patient recall of screening results at a later timepoint	4.0	4	6.8	7

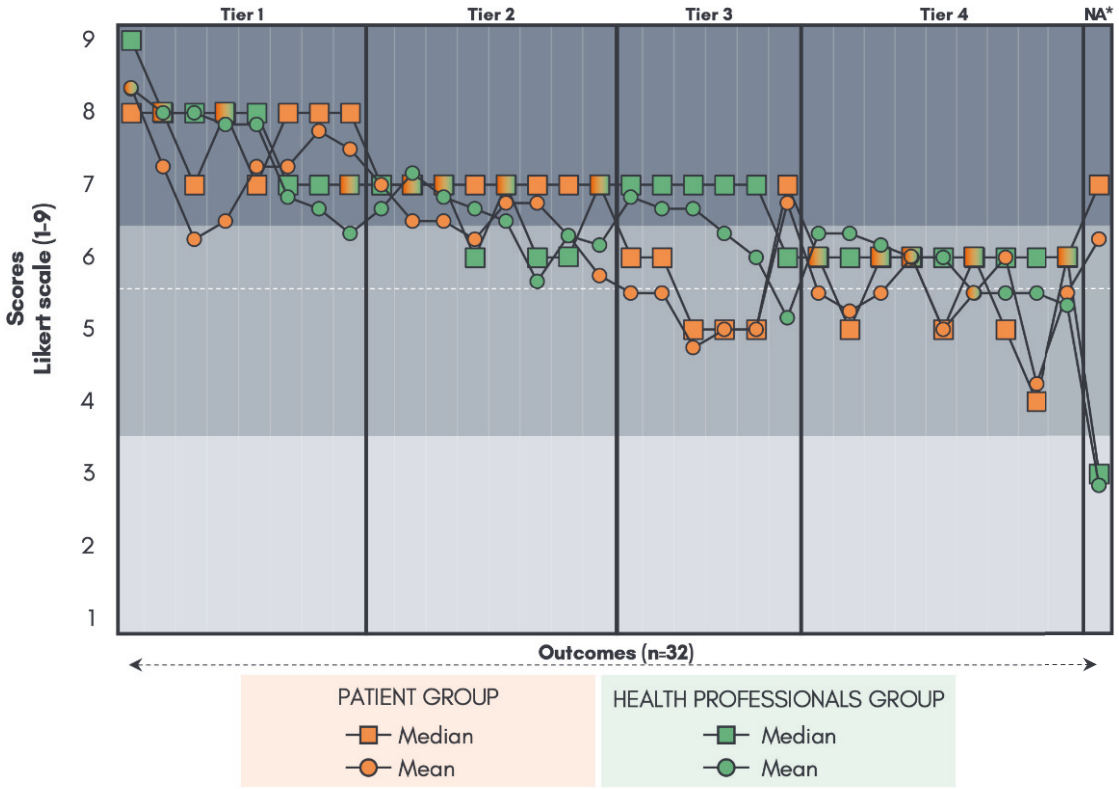
Barriers and facilitators influencing patient understanding	5.2	5	7.2	8
Domain 14 - Acceptability of further testing and alternative reproductive options				
Patient preferences regarding PND, IVF/PGD and TOP	6.0	7	5.0	6
Patient religious views regarding PND, IVF/PGD and TOP	4.8	6	3.8	4
Patient perceptions of the societal acceptability of PND, IVF/PGD and TOP	5.2	6	3.5	4
Domain 15 - Psychological wellbeing				
Impact of results on parental prenatal attachment	5.5	5	3.8	4
Patient-reported anxiety	6.3	7	6.8	7
Grief and loss following an increased risk result	6.5	7	6.5	6
Impact of events (distress) following an increased risk result	6.0	6	7.0	7
Uncertainty and resilience in patients following an increased risk result	6.7	7	7.5	8
Impact of results on patient perception of their own health	6.8	8	6.0	6
Barriers and facilitators to patients psychological and emotional wellbeing during RCS	6.3	7	6.7	7
Domain 16 - Decision satisfaction and regret				
Retrospective satisfaction with the decision to accept or decline RGCS	6.5	7	6.0	7
Decisional regret associated with RGCS	6.7	7	6.2	7
Domain 17 - Privacy and stigmatisation concerns				
Patient concerns regarding stigmatisation	5.0	4	4.7	5
Patient concerns regarding privacy and confidentiality	5.3	5	5.0	6
Patient concerns regarding insurance	5.0	4	4.7	5
Domain 18 - Patient preferences				
Patient preference regarding which condition to include in RGCS	4.7	5	5.3	6

Patient preference regarding how many conditions are included in RGCS	4.7	6	5.2	6
Patient preference regarding ethnicity-specific versus pan-ethnic screening	5.2	5	4.2	4
Patient preference regarding the timing and setting of RGCS	4.7	5	4.5	5
Patient preference regarding the format of results	4.5	5	5.7	7
Patient preference regarding who offers RGCS	3.8	4	6.0	7
Domain 19 - Patient satisfaction with the processes of RGCS				
Satisfaction with accessibility, cost and convenience of the screening process	7.3	7	6.2	7
Satisfaction that information needs have been met	5.8	6	7.0	7
Satisfaction with healthcare providers	5.8	6	6.2	7
Domain 20 - Familial implications				
Dissemination of results to at-risk family members	6.3	6	4.7	6
Impact of results on couple's relationship	7.0	7	5.8	6
Impact of results of family relationships	6.3	7	4.3	5
Support needs for dissemination of results to at-risk family members	5.3	5	5.7	6
Domain 21 - Perceived utility of RGCS				
Reproductive empowerment	6.8	7	7.2	8
Number of affected individuals born to patients who accessed RGCS	8.0	8	6.5	7
Patient perception that the timing of RGCS allowed them to maximise the utility of their results	5.7	6	5.3	5

[a] relevant to studies offering RGCS sequentially, [b] relevant to studies offering RGCS prenatally. Abbreviations: CVS - chorionic villus sampling, IVF/PGD - in vitro fertilisation with preimplantation genetic diagnosis, PND - prenatal diagnosis, TOP - termination of pregnancy

6.5.3 Distribution of Round 2 rankings and definition of tiers of consensus

The mean and median rankings per group for each outcome in Round 2 are shown in Table 9. All outcomes in Round 2 were ranked either "important but not critical" or "critically important" by one or both groups of participants. The distributions of rankings are shown in Figure 16. Based on the results following Round 2, the decision was made to not progress to a third round of the Delphi survey because this would have been unnecessarily onerous on participants and was unlikely to yield additional helpful insights. The distribution of rankings following Round 2 was used to define tiers representing the degree of consensus regarding the importance of each outcome.



Tier 1 – Agreement of critical importance in BOTH groups
Tier 2 – Outcomes with agreement that they are of high importance but not critical in BOTH groups (defined as Mean AND Median 5.5)
Tier 3 – Agreement of critical importance in one group, and important but not critical in the other.
Tier 4 – Outcomes with agreement that they are important but not critical
***No agreement** – Outcomes with discrepant ratings between groups

Figure 16: Distribution of rankings in Round 2

Table 9: Round 2 rankings

CODECS Outcome Domains and Outcome Descriptions	Patient Group		Health Professionals Group	
	Mean	Median	Mean	Median
Domain 1 - Primary laboratory outcomes				
Carrier and couple detection rates	6.3	7	8.0	8
Domain 2 - Secondary or incidental laboratory outcomes				
Identification of secondary or incidental findings	5.5	6	6.3	6
Domain 3 - Technical laboratory outcomes				
Technical laboratory outcomes	6.0	6	6.0	6
Domain 4 - Uptake of services				
Uptake of RGCS	5.5	6	6.8	7
Barriers and facilitators to access and uptake of RGCS	5.3	5	6.3	6
Domain 5 - Genetic counselling resource use				
Uptake of post-test genetic counselling	6.5	8	7.8	8
Domain 6 - Further testing and reproductive decision-making				
Uptake of partner testing[a]	7.3	7	7.8	8
Uptake of PND[b]	7.3	8	8.0	8
Barriers and facilitators related to further testing and reproductive decision	6.5	7	6.8	7
Support needs when making reproductive decisions	5.0	5	6.3	7
Reproductive decisions following an increased risk result	8.3	8	8.3	9
Domain 7 - Pregnancy outcomes				
Results of PND (CVS or amniocentesis)[b]	6.5	7	7.2	7
Rate of fetal loss following PND[b]	6.3	7	2.8	3
Decision to continue or terminate a pregnancy identified to be affected through PND[b]	7.5	8	6.3	7
Results of IVF/PGD utilised by increased risk couples in subsequent pregnancies	6.8	7	5.7	6
Domain 8 - Patient attitudes, perceptions and beliefs related to RGCS				
Patient perception that RGCS will inform their reproductive decisions (at the time of the screening offer)	7.0	7	6.7	7

Domain 9 - Deliberation and informed choice				
Informed choice	5.0	5	6.0	7
Domain 10 - Knowledge and understanding				
Patient understanding of RGCS	6.3	7	6.3	6
Recall of screening result at a later timepoint	4.3	4	5.5	6
Barriers and facilitators influencing patients understanding of RGCS	4.8	5	6.7	7
Domain 11 - Psychological wellbeing				
Patient-reported anxiety	5.5	6	6.2	6
Grief and loss following an increased risk result	5.5	6	5.5	6
Impact of events (distress) following an increased risk result	5.8	7	6.2	7
Uncertainty and resilience in patients following an increased risk result	5.5	6	6.7	7
Impact of results on patients perception of their own health	5.5	6	5.3	6
Barriers and facilitators to patients psychological and emotional wellbeing during RGCS	5.0	5	6.0	6
Domain 12 - Decision satisfaction and regret				
Decisional satisfaction or regret related to RGCS	6.0	5	5.5	6
Domain 13 - Patient satisfaction with the processes of RGCS				
Satisfaction with accessibility, cost and convenience of the screening process	6.8	7	6.5	7
Satisfaction that information needs have been met	6.3	7	6.7	6
Domain 14 - Familial implications				
Impact of results on a couple's relationship	6.8	7	5.2	6
Domain 15 - Perceived utility of RGCS				
Reproductive empowerment	7.3	8	6.8	7
Affected individuals born to patients who accessed RGCS	7.8	8	6.7	7

[a] relevant to specific study designs, [b] relevant to studies offering RGCS prenatally

Abbreviations: CVS - chorionic villus sampling, IVF/PGD - in vitro fertilisation with preimplantation genetic diagnosis, PND - prenatal diagnosis, TOP - termination of pregnancy

6.5.4 Tier 1 outcomes and definition of a preliminary COS

Tier 1 outcomes were those that reached consensus as being of critical importance to include in all future studies. These outcomes were in the CODECS outcome domains (1) primary laboratory outcomes, (2) pregnancy outcomes, (3) resource use, and (4) perceived utility. Within these domains, the prioritised outcomes were (1.1) carrier and couple detection rates, (2.1) uptake of prenatal diagnosis, (2.2) decision to continue or terminate an affected pregnancy, (3.1) uptake of partner testing, (3.2) uptake of post-test genetic counselling, (4.1) reproductive decisions made by patients post-test and long term, (4.2) reproductive empowerment, and (4.3) affected individuals born to patients who accessed RGCS. A preliminary COS based on these outcomes, including the full outcome description, is shown in Figure 17.

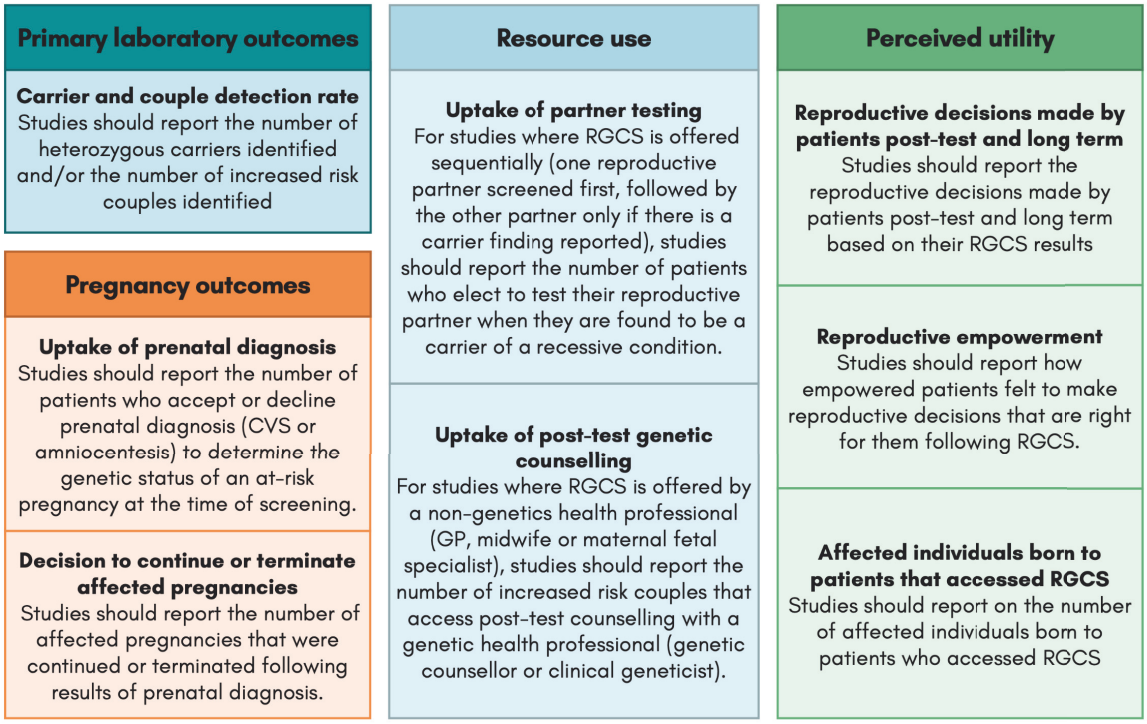


Figure 17: Preliminary COS

Defined by Tier 1 outcomes that reached consensus on critical importance.

6.5.5 Lower tiers of consensus

A list of all outcomes per tier is available in Appendix D.

Tier 2

Five outcomes were grouped in Tier 2 based on their rankings that reflected general agreement across stakeholders of critically importance but failed to reach the consensus threshold.

Tier 3

Nine outcomes were grouped in Tier 3 based on their rankings where one participant group considered them critically important and the other important but not critical.

Tier 4

Nine outcomes were grouped in Tier 4 based on their rankings that demonstrated consensus between groups that they are important but not critical for all future studies to report. The ranking of importance for these outcomes decreased between Round 1 and Round 2. Thirty-six outcomes from Round 1 that were excluded from Round 2 were also included in this tier. These outcomes may represent outcomes that are not considered 'core' with regard to being relevant to all studies of RGCS but have recognised importance for providing information about key aspects of the RGCS process. Such outcomes are appropriate to assess to create an evidence base to address specific research questions but are unlikely to need to be continually assessed once this evidence based is established.

6.5.6 Outcomes with no agreement

One outcome "rate of fetal loss following prenatal diagnosis (CVS or amniocentesis)" was discordant between groups. Comments collected from participants elucidated the reason for the lack of agreement between groups. Health professional participants, who were aware of the literature on this topic from the broader obstetric field, did not feel that this was a direct outcome of RGCS but rather of the prenatal diagnostic procedure, and that sufficient data were available regarding rates of fetal loss. Without this broader context, patients understandably considered this a critical outcome.

6.6 Discussion

Outcomes are the means by which we evaluate the impact and effectiveness of health interventions. The choice of outcomes directly impacts the quality of the evidence available for such evaluations and whether evidence to inform practice and policy is available. The ad hoc definition of outcomes in individual studies is a common theme across the medical literature but leads to questions about why outcomes were chosen, their relevance to all key stakeholders, issues with selection or reporting bias and difficulty comparing outcomes across studies.[28] This study demonstrates the process of systematically defining core outcomes of importance to key stakeholders in RGCS, including patients/prospective parents accessing RGCS, genetic health professionals, researchers and policy-makers.

Consistent reporting of primary laboratory outcomes allows for comparison between studies and provides empirical evidence to guide best practice. Different schools of thought favour (1) couple-based screening, which reports only reproductive risk as a couple or (2) sequential screening, which screens one partner first (typically the female partner) followed by the other partner only if the first partner is reported to be a carrier. The couple-based approach has two benefits. First, it minimises the cost and resources for partner testing and follow-up[29,30]. Secondly, it reduces the chance of the couple misunderstanding their reproductive risks (and potential subsequent anxiety).[31] Issues around the couple-based approach include the inability of individual carriers to inform their at-risk relatives of their carrier status and the need for repeat testing if individuals re-partner.[32] To illustrate how these potential benefits and issues impact stakeholders, we recommend that future research assessing couple-based RGCS report the number of couples identified as increased risk following screening. Studies offering sequential RGCS should report the number of individual carriers and the number of couples at increased risk. Researchers should also consider the associated outcome domain 'Resource use' to report the uptake of partner testing. Partner testing is an important outcome to understand whether offering RGCS sequentially is an access barrier for couples because of the additional time and effort required to present for screening twice. Both couple-based and sequential study types should orient primary laboratory outcomes within their dataset as a percentage of total individuals or couples screened.

The participants in this study considered pregnancy outcomes to be critically important for studies offering RGCS prenatally to report. Although RGCS is ideally offered preconception, for practical reasons a large percentage of patients continue to access RGCS prenatally and practice recommendations support its offer to all women during their

first trimester of pregnancy.[33] There are additional challenges for RGCS in the prenatal setting, including the limited time for decision-making, fewer reproductive decisions available to couples and complexities in ensuring appropriate genetic counselling to differentiate RGCS from other prenatal tests[34]. We recommend that studies report whether increased risk couples elect to proceed with invasive prenatal testing and (where relevant) the decision to continue or terminate their pregnancy. These are foundational outcomes to capture the experience of couples accessing RGCS prenatally. Consistent reporting of these outcomes across all studies will improve the understanding of couples' decision-making and allow for comparisons of decision-making in couples accessing RGCS preconception. These outcomes will help to guide how RGCS is offered in the future and whether additional support is needed for patients accessing RGCS in the prenatal period.

Resource use is a crucial element of scaling RGCS to a population screening offer. The current resource limitations in the genetics workforce are a key element of scaling. A lack of appropriately trained genetic health professionals necessitates the use of non-genetics health professionals as alternative providers to offer RGCS to free up the specialised genetic workforce to manage only increased risk or complex cases.[35] A recent systematic review of the barriers and enablers of the implementation of RGCS identified several barriers centred around the availability of support from a genetic counsellor to non-genetics health professionals.[36] Studies highlighted a mismatch between the resource-intensive and specialised nature of genetic counselling for RCGS in the face of a limited genetic counselling workforce.[37-40] One study found that a median of 64 minutes was required for post-test genetic counselling.[29] Although many outcomes related to resource use were considered during this Delphi survey, participants prioritised the uptake of post-test genetic counselling as a critically important outcome. This outcome reflected the desire to understand the resources required to manage RGCS results when offered through non-genetics health professionals. We recommend that studies offering RGCS through non-genetics health professionals report the uptake of post-test genetic counselling with a genetics health professional (genetic counsellor or clinical geneticist). As RGCS becomes increasingly available, this outcome is critical to understand workforce requirements and to build evidence for increased resource allocation.

The goals of RGCS are innately intertwined with the assessment of utility. Goals describe the intended benefits of RGCS, whereas utility represents the practical assessment of such benefits through the measurement of outcomes. The goals and utility of RGSC are conceptualised in various ways in the literature, and there is no consensus

on the most appropriate outcomes to assess to capture the impact at this overarching level. Approaches have evolved over time; early RGCS screening programs measured utility based on the prevention of genetic conditions and reduction in disease incidence.[11,41,42] However, recent discussions have questioned the ethical appropriateness of such an outcome in the context of general population screening and expanded panels.[43] From a bioethical perspective, reducing disability or disease incidence is problematic and is not recommended as a primary goal of RGCS[44], although it is recognised that this could be considered an important aspect by individual participants in RGCS if their motivations and values reflect a desire to reduce the suffering associated with the unexpected birth of a child with a severe genetic condition. The prioritisation of the outcome 'affected births' in the preliminary COS reported here may reflect the values of the stakeholder participants, and it will be important to consider the appropriateness of including this outcome in a final COS following international consultation with a larger cohort of stakeholders.

The goal to facilitate reproductive autonomy and to enable informed reproductive decision-making is currently favoured[45,46]; however, it remains unclear how to assess the utility of RGCS for reproductive decision-making. A common suggestion is to measure reproductive decisions based on RGCS results, which are often used as a proxy to reflect informed reproductive decisions. However, an 'informed' decision cannot be captured by a simple metric of behaviour. Rather, this needs to be considered from the patient perspective. Previous work highlights patient perceptions that reproductive empowerment most accurately captures the utility of RGCS.[18,19] Empowerment considers behaviour in the wider context of cognitive capacity, knowledge and emotional state.[7] Building on these patient-derived findings, the participants in the study reported here perceived utility as a multifaceted concept requiring the assessment of multiple relevant outcomes encompassing broad societal impact (disease incidence or number of affected births), specific actions (reproductive decisions made by increased risk couples) and the patient perspective (feeling empowered to make reproductive decisions that align with patient values). A definition of utility that is aligned with the evolving goals of RGCS as a population screening program will be a continued focus of the CODECS study in the next stages of the consensus process to define a final COS.

6.7 Limitations

This Delphi survey was limited to Australian and New Zealand participants, and does not represent international perspectives that may deviate from this context. Not all relevant stakeholder groups could be recruited for this Delphi survey because resource limitations hindered the inclusion of non-genetics health professionals such as general practitioners, midwives, and obstetrician gynaecologists who may offer RGCS. The perspectives of these practitioners will be a valuable addition to a future international consensus process. In regard to the conduct of the survey itself, the size of the Round 1 survey was onerous and may have led to fatigue in participants. In addition, the questions were not randomised because a logical approach was favoured give the size of the survey; this may have contributed disproportionately to survey fatigue in the later items/domains, although we note that this was not overtly apparent.

6.8 Conclusion

The outcomes reported herein reflect the perspective of AUS/NZ stakeholders regarding the core outcomes of RGCS that should be reported by all futures studies on this topic. In its current form, this preliminary COS can be used as a guide for future research that wishes to incorporate evidence-based outcomes that can capture the benefits of RGCS, be used as a guide for auditing current RGCS offers and be used as a framework for systematic reviews to evaluate gaps in core evidence on this topic. A future international consensus process is needed to develop these outcomes further and to define a final COS that will be relevant to the diverse settings that RGCS is offered in worldwide. The core outcomes are not intended to represent all outcomes of importance to consider in studies of RGCS but represent a minimum that should be assessed and reported. Studies should continue to include other outcomes of relevance to their research question and context, and should be guided by recent publications that have highlighted important patient-led outcomes of RGCS.[18,19]

6.9 Summary of supporting data available in Appendix D

The following supporting data are available in Appendix D:

Supplementary material D.1 – Protocol changes for the AUS/NZ Delphi process

Supplementary material D.2 – Email invitations to participants

Supplementary material D.3 – Participant information sheet

Supplementary material D.4 – Guidance for participants – Round 1

Supplementary material D.5 – Round 1 Delphi survey

Supplementary material D.6 – Outcomes excluded from Round 2

Supplementary material D.7 – Outcomes eligible for inclusion in Round 2

Supplementary material D.8 – Outcomes combined for Round 2

Supplementary material D.9 – Guidance for participants – Round 2

Supplementary material D.10 – Round 2 Delphi survey

Supplementary material D.11 – List of outcomes per tier following Round 2

6.10 References

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Chapter 7: Synthesis of findings and discussion of the implications for clinical practice and future research

7.1 Chapter overview

In this chapter, I discuss how the findings reported in this thesis address the aims of the Core Outcome Development for Carrier Screening (CODECS) study and provide four key findings. I outline the implications of the findings for future research and clinical practice, address the strengths and limitations of the findings, and summarise the next steps for the CODECS study.

7.2 Addressing study aims

The findings from the CODECS study to date and the corresponding thesis chapters are synthesised with the overall PhD project aims outlined in Chapter 1.

7.2.1 Primary aim 1: To establish an evidence base to support the development of a core outcome set for reproductive genetic carrier screening

A sequential systematic review of quantitative and qualitative studies[1,2] was conducted to establish an evidence base to support the development of a core outcome set (COS) and understand the benefits that a COS could provide to the field of reproductive genetic carrier screening (RGCS). A key indication for a COS is when outcome selection is highly variable in a body of literature, resulting in difficulty comparing and contrasting studies, and contributing to issues of research waste.[3] Indications of bias in the literature and assessing whether outcomes of relevance to patients are incorporated are also important factors to consider to inform the development of a COS.[4] The systematic review of quantitative studies reporting an offer of RGCS found evidence of outcome heterogeneity, indications of biases, and a lack of patient-reported outcomes.[1] Utilising a framework based on the evidence needed to evaluate a screening offer, this review also identified clear gaps in the data available to inform evidence-based practice

recommendations and highlighted the limitations of the current consensus-based practice recommendations.

The systematic review of qualitative studies exploring patient experiences of RGCS found outcomes of importance to patients that were not reflected in the quantitative literature.[2] This indicated that there were key aspects of RGCS not being captured that are likely to be important for implementation as they are of direct concern to patients.

Taken together, these findings provided a strong rationale for the development of a COS and fulfilled the aim of establishing an evidence base to support this undertaking. This thesis research has shown that a COS has the following potential benefits in the setting of RGCS: (1) reducing outcome heterogeneity by ensuring that core outcomes are reported consistently across studies and are available for use in meta-analyses, (2) reducing bias by ensuring the core outcomes at a minimum are always reported and by allowing both significant and non-significant findings to be represented and considered, (3) enhancing the relevance of outcomes to patients as end-users and in doing so maximising the likelihood that research findings can inform practice directly, and (4) ensuring that current gaps in knowledge needed to inform evidence-based practice recommendations are recognised and addressed, thereby reducing research waste by ensuring research efforts are targeted at areas that are crucial for guiding practice.

7.2.2 Primary aim 2: To explore the patient experience of reproductive genetic carrier screening and engage in a co-design process to understand the outcomes of importance to patients

The systematic review of qualitative studies on RGCS[2] and the qualitative interview study[5] focused on the identification of outcomes of importance to patients undertaking RGCS. From the existing qualitative literature, three new outcome domains not previously represented in any quantitative evaluations of RGCS were identified and are discussed below. These established a foundation for further exploration of the patient experience to inform subsequent interviews with patients.[2]

Firstly, the patient experience of pre- and post-test genetic counselling was identified, with outcomes that reflect patient needs during such interactions and how well

these are being met being highlighted by studies. Secondly, the acceptability of further testing and alternative reproductive options was identified. This domain captured the retrospective acceptability of RGCS following the lived experience of undertaking the process from start to finish. Retrospective acceptability is absent from quantitative studies to date that have instead focused on uptake as a proxy for prospective acceptability. However, prospective acceptability is limited to the pre-test period and cannot capture changes in patient perceived acceptability of RGCS based on their experience once results are received and the implications are evident. Lastly, the domain of perceived utility of RGCS related to outcomes that reflected patient perceptions of the impact of RGCS and how they utilised the results. The unique perspective of patients highlighted the need for a consensus definition of outcomes that can capture utility that is relevant to all stakeholders. A commentary based on this finding reiterated the importance of these patient-led outcomes for evaluating the effectiveness of ethically robust RGCS programs.[6] The qualitative systematic review[2] also reiterated the importance of considering adverse outcomes that can occur in the setting of RGCS and the importance of including patients in the selection of outcomes for research to ensure that studies can capture impact accurately.

The identification of new outcomes from published qualitative studies that were not represented in quantitative evaluations of RGCS informed a focused approach to patient interviews that aimed to elicit outcomes of importance directly from those with a lived experience of undertaking RGCS.[5] Using a novel method based on co-design and the nominal group technique, this thesis identified 18 outcomes that were unique to patient interviews and would not have been identified from the sequential systematic review alone. These outcomes highlighted significant gaps in the understanding of the impact of RGCS for patients that can inform future research directions. Five areas of particular interest were previously discussed in Section 5.7 of Chapter 5.

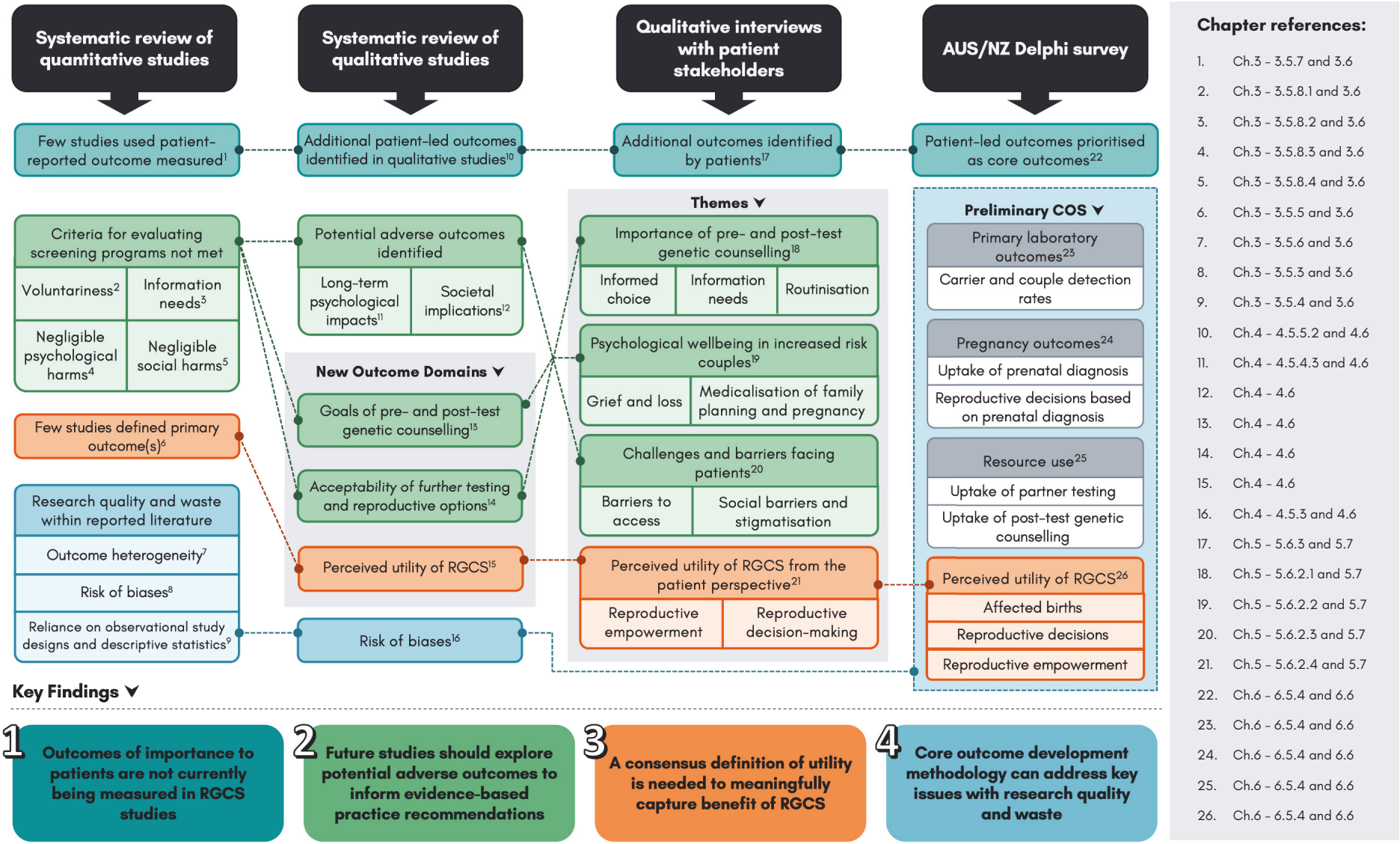
The studies that informed this aim allowed for the identification and incorporation of outcomes directly indicated by patients to be of importance and relevance to their experience. Not all outcomes of importance to patients will be appropriate to include in a COS but can help to guide future research to address specific questions that remain from a policy and implementation perspective.

7.2.3 Primary aim 3 (amended): To understand the level of consensus on the core outcomes that should be measured by all future studies of RGCS

The ultimate aim of the CODECS study is to prioritise the outcomes that are considered by key stakeholders to be critically important for all future studies of RGCS. The Australia and New Zealand (AUS/NZ) Delphi survey produced consensus on eight outcomes across the domains of primary laboratory outcomes, pregnancy outcomes, resource use and perceived utility.[7] These outcomes form a preliminary COS that summarises the findings of the CODECS study to date. There was an overall high level of consensus across all outcomes presented in the Delphi survey, with the importance of most outcomes being rated similarly within and across groups, and only one outcome being discordant between groups. The findings from the AUS/NZ Delphi survey together with insights gained from conducting the survey in this group as a microcosm of the wider context of RGCS, will help to inform a future international Delphi survey and consensus meeting whose aim is to define formally the final COS for RGCS. In its current form, the preliminary COS can be utilised by researchers and clinicians to guide outcome selection for research studies or auditing purposes; this is will be discussed in Section 7.6 (Implications for research and clinical practice).

7.3 Key findings

Herein, I present the four key findings from the CODECS study to date synthesised with relevant literature. An integrated results matrix was used to visualise each project (Chapters 3-6) side-by-side to compare findings across studies and to generate meta-inferences that have informed the key findings reported herein (Figure 18).[8]



Chapter references:

1. Ch.3 - 3.5.7 and 3.6
2. Ch.3 - 3.5.8.1 and 3.6
3. Ch.3 - 3.5.8.2 and 3.6
4. Ch.3 - 3.5.8.3 and 3.6
5. Ch.3 - 3.5.8.4 and 3.6
6. Ch.3 - 3.5.5 and 3.6
7. Ch.3 - 3.5.6 and 3.6
8. Ch.3 - 3.5.3 and 3.6
9. Ch.3 - 3.5.4 and 3.6
10. Ch.4 - 4.5.5.2 and 4.6
11. Ch.4 - 4.5.4.3 and 4.6
12. Ch.4 - 4.6
13. Ch.4 - 4.6
14. Ch.4 - 4.6
15. Ch.4 - 4.6
16. Ch.4 - 4.5.3 and 4.6
17. Ch.5 - 5.6.3 and 5.7
18. Ch.5 - 5.6.2.1 and 5.7
19. Ch.5 - 5.6.2.2 and 5.7
20. Ch.5 - 5.6.2.3 and 5.7
21. Ch.5 - 5.6.2.4 and 5.7
22. Ch.6 - 6.5.4 and 6.6
23. Ch.6 - 6.5.4 and 6.6
24. Ch.6 - 6.5.4 and 6.6
25. Ch.6 - 6.5.4 and 6.6
26. Ch.6 - 6.5.4 and 6.6

Figure 18: Integrated results matrix

7.3.1 Key finding 1 - Outcomes of importance to patients are not currently being measured in RGCS studies

> "The only source of knowledge is experience."
> **- Albert Einstein**

Consistent with this quote by Albert Einstein, this finding highlights that patients are best placed to describe the impacts of a health intervention based on their lived experience. Recognition of the valuable contribution that patients can make is a major development in the recent approach to research and health care. The concept of patient-centred care, also known as patient-oriented or client-centred care, involves the active engagement with patients as partners in the research process and evaluation of healthcare services.[9] Major efforts reflect the perceived value of patient-centred approaches to health and research internationally, including the Patient-Centred Research Network (PACER Network) in Australia,[10] the National Institute for Health Research (NIHR) in the United Kingdom,[11] the Patient-Centered Outcomes Research Institute (PCORI) in the United States,[12] and the Strategy for Patient-Oriented Research (SPOR) in Canada.[13] Each of these initiatives recognises the benefits of understanding the patient perspective to increase the relevance of research and the likelihood that research findings reflect real-world needs and can inform practice directly.[12]

Guidance for developing a COS prioritises patient involvement and considers it a fundamental aspect of developing a high-quality COS.[4,14] Ensuring that patients have a say in which outcomes are included in a COS maximises the likelihood that research findings can demonstrate clearly whether the health intervention has benefited patients or not. Conversely, excluding patients from the COS development process is likely to result in the omission of important outcomes and production of research that cannot definitively demonstrate benefit and is wasteful.[15] Numerous examples indicate the value added by patient involvement in COS development, such as the identification of outcomes of importance to patients that have been overlooked by researchers and clinicians or that were seen as being of limited value before patient involvement.[16,17]

Outcome Measure in Rheumatology (OMERACT), which was established in 1992, is one of the longest-running COS development initiatives.[18] OMERACT has shown the

significant positive impact of involving patients in outcomes research. Based on over 20 years of working with patient research partners, they have shown that patients 1) widened the research agenda and identified new research directions, 2) identified new patient-led outcomes for COS not previously considered, 3) contributed to the development of measurement tools to capture patient-reported outcomes or improve existing measurement tools, 4) changed the wider culture of OMERACT and established trust, respect and understanding that facilitated enriched communication, and 5) encouraged change outside of OMERACT in the wider outcomes research community by disseminating their experience and participating in other efforts such as the Core Outcome Measures in Effectiveness Trials (COMET) initiative.[19]

Considering this wider context of patient involvement in research broadly as well as in the development of core outcome sets, the finding that patients identified outcomes of importance that were previously unexplored or underexplored is consistent with our expectations at the inception of designing the CODECS study. The significant body of evidence demonstrating the benefit of using patient-led outcomes to improve the overall quality of research across many diverse health interventions in the COS literature suggests that similar benefits can be gained by prioritising the patient-led outcomes identified by this study. There are two main types of outcomes of importance to patients undertaking RGCS that we identified here: 1) outcomes that were prioritised as core outcomes in the AUS/NZ survey and therefore reflected outcomes that participants considered that all future studies of RGCS should assess, and 2) outcomes that may not be core outcomes but may represent research gaps and can help to guide future research to understand the impact and inform implementation.

One of the eight outcomes that reached consensus as being critically important to include in a COS in the AUS/NZ Delphi survey was the patient-led outcome of empowerment.[7] Empowerment is defined as a construct that encapsulates five concepts: (1) decisional control (2) cognitive control (3) behavioural control (4) emotional regulation and (5) hope.[20] The outcome of empowerment would not have been included in the Delphi survey without the prior steps of incorporating patient perspectives through the systematic review of the qualitative literature[2] and patient interviews[5] conducted for this study. Empowerment as a concept is widely discussed in the RGCS literature, but it has not been incorporated into any quantitative evaluations of RGCS. Recognising the importance of empowerment to patients and making the efforts to assess it empirically

may provide new insights and demonstrate more definitively the benefits of RGCS as it is implemented at population scale.

Of the other patient-led outcomes identified throughout this study, many were considered important but not critical for inclusion in a COS in the AUS/NZ Delphi survey; these are outlined in Appendix D (Supporting evidence for Chapter 6). Such outcomes reflect areas that are underexplored or have not been considered in research to date and would benefit from well-designed and rigorously conducted studies to capture and assess them. Ongoing measurement of such outcomes is unlikely to be needed, but establishing a strong evidence base to understand how these outcomes are impacted when RGCS is offered at population scale would provide the foundation needed to inform patient-centred implementation.

7.3.2 Key finding 2 - Future studies should explore potential adverse outcomes to inform evidence-based practice recommendations

> "*Primum non nocere* – first do no harm."
> **– The Hippocratic oath**

The Hippocratic oath binds clinicians to a set of moral standards and guides their practice of medicine.[21] Here, I consider the concept of "first do no harm" a widely recognised principle from the Hippocratic oath that relates to the prevention or minimisation of adverse outcomes from health interventions. Although this oath is often cited in relation to clinicians, the ethical principles underpinning it also apply to allied health professionals and researchers working in healthcare and are considered in practice recommendations and policy decisions. Practice recommendations are an important way for professional organisations to signal to their members what health interventions are appropriate to offer and balance evidence on the benefits and harms of an intervention to determine whether it should be offered. The evidence used to inform practice recommendations can vary greatly depending on how much is known about the intervention, the volume and quality of research that has been conducted and professional and stakeholder opinions on the benefit of the intervention. Grading systems are used to indicate the type and quality of evidence used to inform practice recommendations.[22,23]

In the setting of RGCS, major professional organisations from the USA, Canada, Australia and New Zealand recommend the offer of RGCS to all women planning a pregnancy or in their first trimester.[24-26] These recommendations currently use expert consensus as their primary source of evidence and are based largely on the demonstrated benefits of RGCS in increased risk groups and the belief that similar benefits could be obtained at population scale. In reality, little empirical evidence is available to demonstrate the benefits of population-based RGCS, and there are differences between targeted and population-based screening settings that could contribute to vastly different outcomes between these groups.[27] These differences are not likely to change the widespread support for RGCS, but it is important to recognise that further research is needed to inform the implementation of population-based offers, maximise benefit and minimise harms. Some key differences discussed here include the larger number of couples that will undertake screening with a focus on the psychological considerations relevant to increased risk couples, and the differing social considerations that are in play at population scale including equity and the way in which RGCS informs wider societal perceptions of genetic conditions and disability.

When considering what constitutes an adverse outcome of genetic testing broadly, the focus tends to fall on psychological outcomes and the concern that genetic testing may result in anxiety or stress that would outweigh the benefits or require additional supports in place to minimise.[28] Most assessment of psychological impact as an adverse outcome of genetic testing has been explored in the context of cancer[29] and Huntington's disease[30]. The balance of benefit and harm in such clinical settings is similar to that of RGCS, but there are some marked differences to consider, including how prepared patients are for increased risk results and how this may affect their coping.

In the systematic review of quantitative studies reporting RGCS,[1] all of the studies that incorporated patient-reported outcomes included one or more psychological outcomes. The most commonly assessed outcome was anxiety, although there was significant heterogeneity; 10 different outcomes were assessed, timepoints of assessment varied and studies lacked consistency in the measurement method used and whether the chosen methods were validated. There was a clear lack of consensus about the most appropriate outcomes to assess to capture the psychological impact of undergoing RGCS. Furthermore, most studies that have reported psychological outcomes were in low-risk couples due to insufficient numbers of increased risk couples being identified. Whereas the findings from these studies demonstrated short-term anxiety and worry that

resolved soon after receiving a low-risk result,[31] assertions of negligible psychological harms following RGCS are currently applicable only to low-risk couples and may not be generalisable to increased risk couples or to the more diverse groups that will be covered by population-based RGCS.

The systematic review of qualitative studies[2] identified numerous psychological outcomes, some of which overlapped with outcomes that have been assessed quantitatively, whereas others were new outcomes that have not been previously considered by research to date. Most notable was the outcomes of grief and loss in increased risk couples. Qualitative studies have explored psychological wellbeing in increased risk couples, which has filled a gap in understanding from quantitative studies; however, despite the descriptions of adverse psychological outcomes including complex grief, such outcomes have not been subsequently incorporated into quantitative evaluations of RGCS. Grief as a relevant psychological outcome was further indicated in the qualitative interviews with patients,[5] in which grief was described as the predominant emotion following an increased risk result that often persisted into the long term. The lack of representation of the relevant psychological outcomes in the literature limited the ability to anticipate potential adverse outcomes for patients undertaking RGCS and to initiate appropriate supports and services in place to minimise the likelihood of long term adverse psychological impacts.

Other posited potential adverse outcomes of RGCS relate to the social context in which population screening takes place. Differing from clinical settings, which focus on the individual and the family, a population screening offer has wider implications at a societal level. A recent scoping review mapped the potential adverse social implications of RGCS including medicalisation of family planning and pregnancy, routinisation, stigmatisation and discrimination, and barriers to equitable and equal access.[32] Potential positive social implications were also considered. Of note, this scoping review identified little to no empirical evidence of social implications across the RGCS literature, which indicated that both negative and positive implications are currently largely theoretical and that there is a need for research in this area to capture the reality of such social implications.

The systematic review of qualitative studies[2] and qualitative interviews with patients[5] identified outcomes that corresponded to the perceived negative social implications as described in the aforementioned scoping review. Implementation of RGCS must recognise the societal factors that affect the patient experience, from access

through to the capacity to make reproductive decisions aligned with their values if identified to be at increased risk.[27] It is crucial that future research includes outcomes that can capture the social implications of RGCS to inform the socially responsible implementation of population-based RGCS and mitigate any potential adverse social implications that could detract from the benefits that RGCS offers.

Potential adverse outcomes of a psychological or social nature are an important finding of the CODECS study. Criteria evaluating the appropriateness of screening offers originated with Wilson and Jungner[33] and expanded to incorporate considerations specific to genetic testing.[34,35] An important element of these criteria is the concept of negligible harms. This concept essentially balances demonstrated or perceived benefits against the real or potential harms of an intervention. Practice recommendations use such criteria to determine whether to endorse a health intervention. Unless appropriate outcomes that can capture potential harms are being assessed, the reliance on consensus-based recommendations to support RGCS will continue. However, future research that addresses this gap in knowledge will help clinicians and researchers to work towards the goal of rigorous, evidence-based practice recommendations that position patients at the forefront of care.

7.3.3 Key finding 3 - A consensus definition of utility is needed to meaningfully capture benefits of RGCS

> "Realise that everything connects to everything else."
> **– Leonardo Da Vinci**

Here, I consider how this quote relates to the perception of utility in health care and how utility is often a multifaceted concept that connects the needs of multiple stakeholders. The conceptualisation of utility and approaches to defining and measuring it are diverse within the healthcare literature. Many terms are used interchangeably – benefit, value, utility – each representing the way one balances the intended benefits with potential harms to inform decisions about the offer of a health intervention.[36,37] In this thesis, I have presented evidence to demonstrate the lack of a clear definition of utility of RGCS and have identified several outcomes that represent perceived utility from different stakeholder perspectives. Situating this lack of clarity within the literature on utility in

genetics and genomics broadly can provide some insight into the next steps towards a clear definition of utility for RGCS.

Approaches to evaluate genetic tests have been discussed widely in the literature, and a 2018 systematic review identified 29 evaluation frameworks published between 2000 and 2017.[38] Most of these studies drew on the Analytic Validity, Clinical Validity, Clinical Utility and Ethical, legal and social implications (ACCE) framework,[39,40] and fewer have referenced the Health Technology Assessment (HTA)[41] process or the Wilson and Jungner screening criteria.[33] The ACCE framework comprises four evaluative domains as specified by its full title and is the main conceptual frame used for the evaluation of genetic tests. Of the four domains that make up the ACCE framework, clinical utility is the one that garners the most attention and is the focus here.

The conceptualisation of clinical utility in genetics is complex.[42,43] The ACCE framework defines clinical utility as "the likelihood that the test will lead to an improved outcome".[39] This definition incorporates evaluation of the risks and benefits of the intervention, and demonstration that it adds value for patient decision-making.[44-46] Although this is a helpful starting point, it is a broad definition that provides little in the way of concrete guidance about how best to assess clinical utility.[47] Concepts of personal and perceived utility[5] to capture aspects that may be beyond the scope of previous definitions of clinical utility are often referred to as separate concepts from clinical utility in the literature. However, an expanded definition from the American College of Medical Genetics (ACMG) suggests that these personal perspectives should be incorporated into the conceptualisation of clinical utility and should not be considered separate or 'less than'.[48] Conceptualisation of clinical utility in such an expanded manner highlights the importance of considering clinical utility from the perspective of the individual, the family and at a societal level.

A recent scoping review examined the conceptualisation of utility across the genetic and genomic literature, and identified 194 studies conducting research to demonstrate the clinical utility of a genetic test.[49] This review identified heterogenous approaches to how clinical utility was conceptualised and assessed, both across the entire dataset and within studies in the same area. The authors concluded that standardised approaches to measuring clinical utility are needed to enable more robust evaluations of genetic tests; this conclusion is also supported by other authors in the field.[38,45,47]

The systematic review of quantitative studies[1] found that only 8% of studies defined a primary outcome or outcomes, a finding that reflects the lack of clarity regarding how the outcomes assessed were intended to demonstrate clinical utility. This review highlighted affected births and reduction in disease incidence, informed reproductive decision-making, and the timeliness of RGCS results as aspects of clinical utility. The systematic review of qualitative studies[2] defined a new outcome domain 'perceived utility of RGCS', which captured outcomes related to how patients conceptualise the value of RGCS. Two main aspects of utility were reflected: a sense of confidence or empowerment in reproductive decision-making and timeliness of results to allow sufficient time for deliberation and decision-making. This patient perspective was expanded on in our qualitative interviews with patients,[5] which highlighted reproductive decisions made based on results, reproductive empowerment and timeliness as key elements of patients' perceived utility of RGCS. Lastly, in our Delphi survey of AUS/NZ stakeholders,[7] the domain of 'perceived utility of RGCS' was prioritised for inclusion in a COS. Within this domain, three outcomes mentioned previously were considered critically important: affected births, reproductive decisions and reproductive empowerment.

To conceptualise clinical utility appropriately, one must consider the goals of RGCS programs and how these can be operationalised as measurable outcomes. A clear definition of the goals of RGCS will help in determining how the program is evaluated and what measure(s) of value reflect success.[50] Recent bioethical explorations of RGCS have highlighted the complexity of defining the goals of RGCS as it expands to a population screening offer.[27] In considering this bioethical perspective, Dive et al. favour a value pluralistic approach, which suggests that it is appropriate for RGCS to have multiple goals that reflect the impact of RGCS on both the couple undertaking screening and their family, and at a wider societal level. This view is consistent with the literature on the conceptualisation of clinical utility as previously described, as well as evidence reported herein that stakeholders conceptualise clinical utility as a multifaceted construct that requires multiple outcomes to capture the full spectrum of value attributed to undertaking RGCS.

The findings of this thesis inform a clearer understanding of clinical utility in the setting of RGCS, although further work is needed. Consistent with suggestions from the genetics literature, a consensus definition of utility informed through multidisciplinary stakeholder consultation and a standardised approach for how to measure utility is needed to ensure that all relevant benefits of RGCS are captured.

7.3.4 Key finding 4 - Core outcome development methodology can address key issues with research quality and waste

> "The answers are all out there, we just need to ask the right questions."
> **- Oscar Wilde**

Asking the right question, or assessing the right outcomes, is a crucial aspect of research that influences the quality and relevance of findings. Here, I consider how COS as a methodology can be used to determine what the 'right questions' are when evaluating genetic health interventions. There are two notable examples of COS methodology being utilised to understand broadly the outcomes of genetic counselling and clinical genetic services that have established a wider culture of outcomes research within the genetics field and informed the approach taken in this thesis.

Firstly, McAllister et al. have numerous studies registered in the COMET database related to their work on exploring the outcomes of clinical genetic services (CGS).[51–57] Initiated because of the recognised need to improve approaches to evaluating CGS, their work has focused on understanding the impact of accessing CGS for patients and families[58,59] and how this relates to measurable outcomes.[60,61] This work led to the definition of empowerment as a key outcome of CGS[62,63] and efforts to establish a theoretical underpinning for empowerment as a construct.[64–66] Operationalising this further, McAllister et al. developed the Genetic Counselling Outcomes Scale (GCOS-24), which is a validated patient-reported outcome measure to capture empowerment.[20] Various adaptations of the GCOS-24 are used in several countries including Denmark,[67] Spain,[68,69] Singapore,[70] Brazil,[71] and in specific settings including autism spectrum and similar disorders.[72] A short-form version of the GCOS-24 titled the Genomic Outcomes Scale (GOS) was developed for increased ease of use.[73] Such work was conducted with a high degree of rigor and established important metrics for validated measurement tools including the minimum clinically important difference for GCOS-24[74] and understanding the sensitivity to change in the GOS.[75] The registration of the work by McAllister et al. in the COMET database indicates a similar ethos behind this work and the development of COS. Many of the methods used, including systematic reviews of outcome measures and eliciting of outcomes from patient and health professional stakeholders, reflect similar goals to a COS development study. Their work has a strong focus on incorporating a

patient-centred approach to the evaluation of CGS and is illustrative of the positive impact that an evidence-based and rigorous approach to establishing meaningful outcomes can make to the genetics field.

Secondly, Zierhut et al. registered the development of a COS for practice in the COMET database aimed at elucidating genetic counselling outcomes from the perspective of genetic counsellors and cited focus groups and a consensus conference as the principal methods used.[76] The authors conducted semi-structured focus groups at the National Society of Genetic Counselors 2013 Annual Education Conference, which recognised the need to define and categorise outcomes of genetic counselling to meet the requirements of value-based healthcare settings. The findings of these focus groups informed the development of 12 outcome-related themes that represented genetic counsellors' perception of the impact and value of genetic counselling in the healthcare system.[77] Similar to the CODECS study, the study by Zeirhut et al. found that some of the outcome themes that were most common in their focus groups were absent or uncommon in the genetic counselling literature at the time, suggesting that these may be outcomes worth considering in the future.

This early exploratory study by Zeirhut et al. has informed a subsequent large body of work, including a systematic review to capture outcomes previously measured in evaluations of genetic counselling,[78] engagement with professional organisations to address issues of quality in the evaluation of outcomes, reporting of genetic counselling interventions and creation of recommendations for standardisation,[79] development and revision of the Framework for Outcomes of Clinical Communication Services in Genetic Counselling (FOCUS-GC) to facilitate the categorisation and organisation of outcomes and their relationship with the process of genetic counselling.[80,81] exploration of racial and ethnic differences and the role of diversity in influencing outcomes of genetic counselling,[82] and a Delphi survey to determine the prioritisation of 181 genetic counselling outcomes across stakeholder groups (including patients) to inform which outcomes may be most important to focus on when evaluating genetic counselling.[83] This ongoing work continues to show the value of a structured approach to outcomes assessment in genetic counselling and the goal of developing a strong evidence-base to demonstrate the benefit that genetic counsellors contribute as a profession to health care.

Although the work of McAllister et al. and Zierhut et al. reflects many of the same methodologies and approaches to outcomes used in COS development, the authors have not referred to the definition of a COS as the goal of their research. The reasoning

behind this may include aspects such as not wanting to dictate a core set of outcomes that all future studies should assess to avoid placing an onerous expectation on researchers and clinicians or appreciating that the outcomes of genetic service use and genetic counselling may be too broad and diverse to trim to a list of five to seven core outcomes. Such reasoning was considered at the inception of the CODECS study and the latter in particular informed the approach to adapt COS development to a specific genetic health intervention; RGCS. This approach would allow insight into whether a targeted approach to outcomes may be appropriate to reduce in the breadth and depth of outcomes that need to be considered.

This thesis represents a valuable addition to previous efforts to address the complex issues of defining and prioritising outcomes in the genetics field. The results of the AUS/NZ Delphi survey[7], which achieved consensus on eight outcomes of critical importance, suggests that the targeted approach taken herein to address outcomes of RGCS may be appropriate when applied to other genetic specialties or types of testing.

7.4 Conclusion

Using COS development methodology, I have captured the current outcomes landscape for RGCS, identified outcomes of importance to patients that have not been evaluated previously, and proposed a preliminary COS to inform future efforts to evaluate RGCS offers. The evolving context of RGCS as it expands to a population-based screening offer has been considered throughout this thesis and is a central consideration for future research. Significant gaps in the evidence base for population-based RGCS have been highlighted and will be important to address in an ongoing manner. The selection of outcomes – the 'what to measure' – is crucial to ensure that research measures what matters and that the benefits and potential harms of population-based RGCS can be captured. A systematic approach to the definition and prioritisation of core outcomes of RGCS is key to minimising research waste and ensuring that future studies work towards a common goal of evidence-based practice recommendations to guide implementation of population-based RGCS and to ensure best care for patients.

7.5 Strengths and limitations

The strengths and limitations of each study are provided in their respective chapters. Here I provide an overview of the strengths and limitations of this thesis.

7.5.1 Strengths

Situating this thesis within an established methodology for the development of a COS as defined by the COMET initiative facilitated a systematic and rigorous approach to address the study aims. A key initial component of this methodology was the development and reporting of a protocol for the intended approach to develop a COS for RGCS. The open access publication of a protocol[84] allows for transparent evaluation of the methodology used to work towards a COS for RGCS, facilitates reproducibility for future review and revision of the COS, and establishes the CODECS study as a reputable undertaking that can facilitate future collaborations. The registering of the CODECS study in the COMET database will help to guard against duplication of efforts or research waste for others interested in this same research area. It can also facilitate the uptake and implementation of the final COS when defined. I adhered closely to the available recommendations for conduct of the CODECS study and followed the framework described by the COMET initiative (summarised in Figure 19) to ensure the greatest possible degree of rigor for this work.

The expertise of the Study Management Group and Study Advisory Group are significant strengths of this thesis, with the ability to tap into expertise related to research methodology, the offer and evaluation of RGCS, and the patient experience of RGCS. The involvement of a patient research partner was helpful for ensuring that the qualitative interviews and Delphi survey were appropriately pitched to facilitate patient understanding and ensure the best possible contribution of patient participants. I undertook a range of training to develop the skills needed to conduct this study, including attending a three day Cochrane systematic review workshop and a University of Technology Sydney seminar series on qualitative methods.

The focus on a patient-centred approach to this thesis is another major strength, with recognition from early in the study design that patient research partners and patient participants would be crucial. Specific to this goal, the development of a novel method to elicit outcomes from patient participants in qualitative interviews that was grounded in the principles of co-design allowed for the generation of rich data to understand the patient experience of RGCS. Orienting these discussions with patient participants in the outcomes setting and trusting that they had the capacity to engage directly with the conceptualisation of outcomes limited the ambiguity in interpreting the outcomes that were important to participants. Guidance for conducting qualitative research in COS

development is currently limited, and the open access publication of this methodology[5] will allow other COS developers to use this method.

Finally, the findings presented in Chapters 2-5 have been published and subject to peer review. Chapter 6 is currently under consideration by the *European Journal of Human Genetics*. Engaging with the peer review process and valuing the contribution of reviewers to improving these studies are important components of my development as an early career researcher.

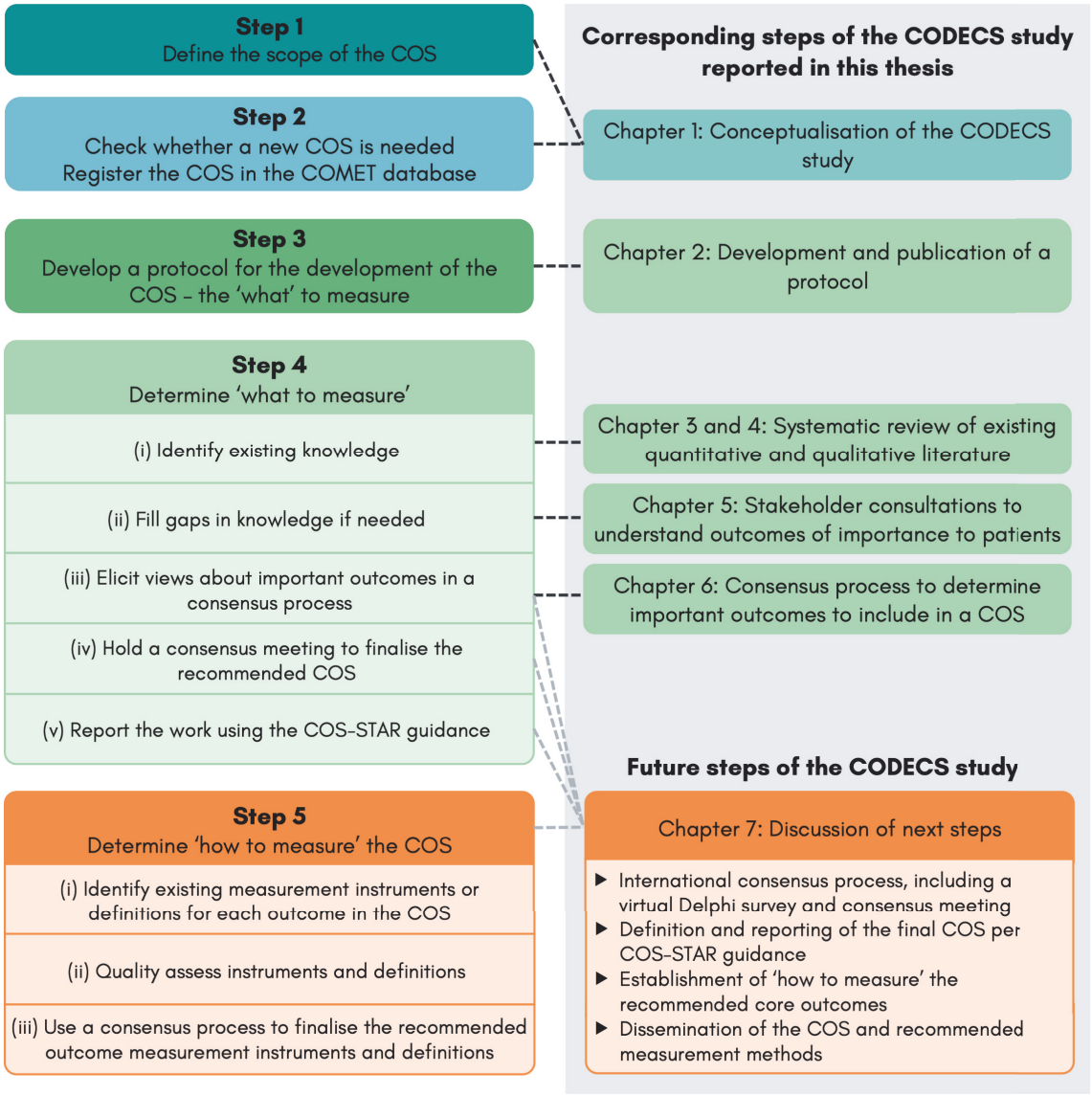


Figure 19: Overview of the steps involved in developing a COS correlated with corresponding steps of the CODECS Study
Adapted from the COMET Handbook[4]

7.5.2 Limitations

Despite efforts to capture an international perspective throughout the CODECS study, this remained limited (Figure 20). The greatest representation was in the systematic review of quantitative studies[1], in which 15 countries were represented. The sequential systematic review of qualitative studies[2] identified evidence from six countries. Participants in our qualitative interviews study[5] resided in five countries, and the Delphi survey[7] was limited to Australian and New Zealand stakeholders. The planned international consensus process would have enabled greater diversity, but it was not feasible within the scope of this PhD. Ensuring that a COS is relevant across all countries that offer RGCS is crucial for implementation and uptake.[15] Any factor that limits uptake will also limit the potential benefits that a COS can have for addressing systemic issues with heterogeneity and bias in the literature. Therefore, ensuring an inclusive international consensus process will be crucial as the next step of the CODECS study.

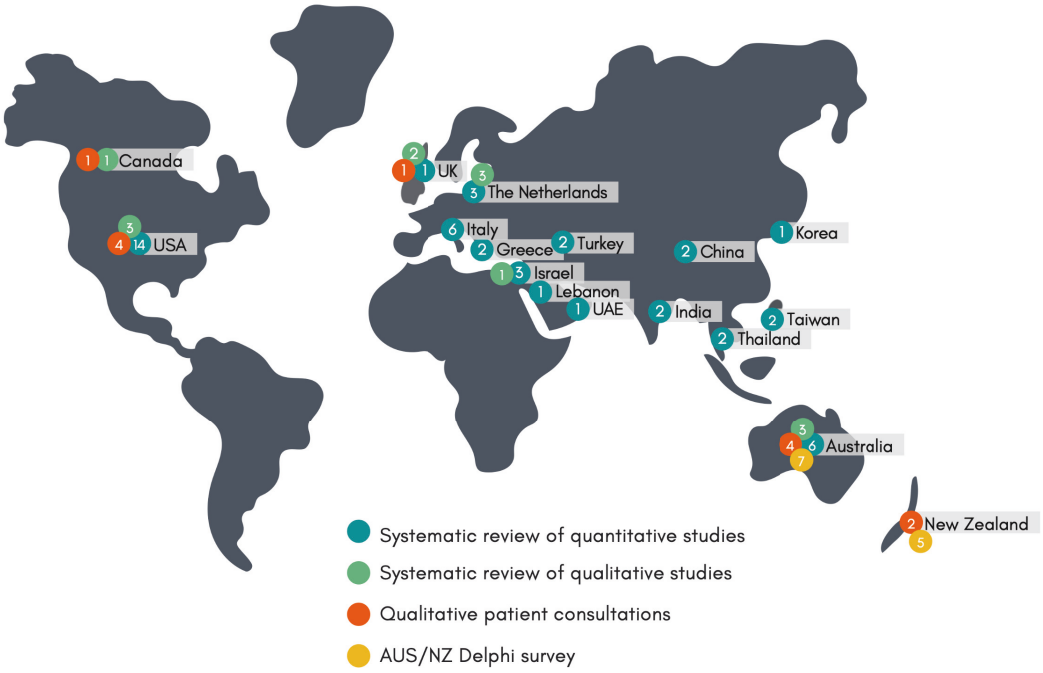


Figure 20: International representation across studies

The impact of COVID on this thesis is also a limitation. Travel restrictions and lockdowns limited my capacity to travel and disseminate information about this study. Although I attended many conferences virtually and submitted abstracts for consideration, the lack of face-to-face attendance limited the ability to build engagement and connections with other like-minded researchers. The conduct of a

successful international consensus process with stakeholders that are engaged with the development of a COS for RGCS will require relationship building and collaborations to establish the reputability of the CODECS study and encourage participation. Limited opportunities for such rapport building have been available but would be of significant benefit for the next steps of the CODECS study.

7.6 Implications for research and clinical practice

This section expands on the key findings reported in this chapter and consider the implications for these findings for future research and clinical practice.

7.6.1 Implications for future research

The findings from this thesis have several implications for future research.

Consideration should be given to the outcomes used in future studies

Outcomes of importance to patients that have not been captured quantitatively should be considered in future studies aimed at evaluating RGCS to ensure that there is a robust evidence base to capture the impact and value of RGCS for patients. These outcomes include grief and loss as a key psychological outcome in increased risk couples, and empowerment as a key outcome for patients' perceived utility of RGCS. Potential adverse outcomes are also important to consider because the evidence for negligible harms have limited generalisability to the expanded context of a population-based screening offer. The social implications of RGCS and outcomes to capture these are underexplored but represent an important component of a population-based RGCS and, as such, should be considered in future studies. The goals and clinical utility of population-based RGCS should be clearly established, and the primary outcomes intended to capture whether these goals have been met/demonstrated should be stated clearly in published studies.

The preliminary COS can be used by researchers in its current form

The preliminary COS defined in Chapter 6 has several functions in the intermediatory period until a final COS can be defined. The preliminary core outcomes represent an evidence-based approach to the selection of outcomes for future studies evaluating RGCS. While these are not yet recommended to be measured by all future studies, researchers can consider the efforts to date that have informed this list and balance the

benefits of assessing these outcomes in their study. Efforts to conduct a systematic review of population-based RGCS offers can also use the preliminary COS to determine whether current studies capture the full scope of outcomes needed to assess the value of RGCS.

COS can be used to meet the requirements of value-based healthcare systems
Considering the wider genetics research setting beyond RGCS and given the increasing recognition of the need for a systematic approach for defining the outcomes of genetic health interventions within value-based healthcare systems, I propose that COS methodology would be a valuable addition to researchers' 'toolkit'. Establishing a community of like-minded researchers will be an important step if COS methods are to be more widely taken up by the genetics community.

COS developers can apply the novel method for eliciting outcomes from patient stakeholders
This thesis also has implications for the community of COS developers seeking guidance regarding how best to elicit outcomes of importance from patient stakeholders. Although some broad guidance is available, specific practical advice for the conduct of qualitative studies as part of a COS development study is lacking. The novel method of eliciting outcomes from patient stakeholders[5] reported in this thesis has been disseminated with clear theoretical underpinnings for the method and with a detailed explanation of each stage of the interview and has been made available with an open access copy of the interview schedule as supplementary material. Future COS developers can review and consider this method for use in their own studies.

7.6.2 Implications for clinical practice

Several implications for clinical practice are also evident.

Outcomes identified can help to fill current gaps needed for development of evidence-based practice recommendations
The implementation of RGCS as a broadly available, population-based screening offer is currently informed by consensus-based practice recommendations. This reliance on consensus-based recommendations highlights the gaps in our understanding of the benefits and potential harms of RGCS. Ultimately evidence-based practice

recommendations should be a goal for the future of RGCS. The outcomes identified in this thesis and the proposed preliminary COS can be used to establish an evidence base that fulfils criteria for development of evidence-based practice recommendations.

Clinicians should recognise the limitations in current evidence

Clinicians implementing RGCS into their practice should recognise the limitations of current practice recommendations and exercise caution to ensure that patients receive the best care. The psychological outcomes identified in this thesis, in particular, the potential adverse outcome of grief and loss should be considered in clinical settings. The coping and psychological wellbeing of patients, especially increased risk couples, should be identified on an individual basis, and risk factors for grief should be managed and, where appropriate, referral arranged to facilitate coping.

Preliminary COS can be used for auditing of clinical RGCS offers

The preliminary COS defined in Chapter 6 can be used as an audit tool in clinical services currently offering RGCS. The outcomes proposed can form a framework to ensure that core outcomes of importance are being captured to evaluate and improve service delivery.

7.6.3 Next steps of the CODECS study

The CODECS study to date has provided much needed clarification regarding the outcomes of RGCS; however, this work has also highlighted the need for further work including the following:

- Conducting an international consensus process to enhance the generalisability and usability of the COS
- Exploring measurement methods for the core outcomes identified and identifying gaps for development or adaptation of current tools to ensure that core outcomes can be captured accurately
- Supporting researchers and clinicians to implement the COS into their future research studies and to use the COS for evaluation of clinical services.

I intend to seek funding and resources to continue with this work in a post-doctoral capacity or for a future PhD student to take on with supervisory advisement from myself and other members of the Study Management Group.

7.6.4 Contributions to the field

Broad significance of this thesis

When I began my candidature in February 2019, this was an emerging area of research with limited studies on the outcomes of population-based RGCS offers and little recognition of the importance of determining the most meaningful outcomes to capture the benefits of RGCS at population scale. Now, there is a much greater recognition of the importance of outcomes and selecting the most appropriate outcomes to maximise research efforts and reduce research waste. The societal context of RGCS has also undergone significant changes since the start of my PhD as previously mentioned in Chapter 1. In Australia, a key development is the government funded Mackenzie's mission initiative, which trialled a publicly funded approach to population-based RGCS.[85] The availability of RGCS in a way that overcame many of the existing barriers to access, including cost, significantly raised public awareness of and interest in RGCS. In contrast to this innovative approach to offering RGCS, the overturning of Roe vs Wade in the USA raised major concerns regarding the undermining of the goals of RGCS in states where couples' reproductive options are now limited and reproductive autonomy is infringed upon.[86] As the societal context of RGCS continues to shift, progressing in some instances and regressing in others, being equipped with appropriate outcomes to capture the impact of RGCS will be vital in the future.

Dissemination and impact of the thesis to date

A protocol and the studies presented in Chapters 2-5 have been published, and the final manuscript presented in Chapter 6 is currently under consideration. The impact of my work is demonstrated by the citations that these publications are starting to accrue. The development of a core outcome set for reproductive genetic carrier screening has received support, for example Van Steijvoort et al. stated, "*we agree with Richardson et al.[84] that a core outcome set is needed to avoid heterogeneity in outcomes and methods of measurement. This will indeed lead to more good quality research evidence that can be used to support the responsible implementation of RGCS and to inform policy makers.*"[87] The rationale I present for development of a COS, including the variability in selection of outcomes and measurement methods, and the associated impact on the ability to compare outcomes across studies has also been referenced.[88] The importance of incorporating outcomes of importance to patients to establish ethically robust RGCS programs was discussed in a commentary[6] following the publication of the systematic

review of qualitative studies.[2] The findings related to potential societal implications of RGCS and the lack of evidence available to evaluate these reported in the systematic review of qualitative studies[2] and qualitative interviews with patients[5] have been referenced in a recent scoping review.[32] My work has also been recognised through an invitation to present a webinar in the Australasian Society of Genetic Counsellors (ASGC) specialist series. I have presented poster presentations annually at the Human Genetics Society of Australasia (HGSA) conference and was awarded the ASGC best poster presentation in 2022.

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Appendix A – Supporting information for Chapter 3

Summary of Content

Supplementary material A.1 – Illustrative search strategy

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Supplementary material A.1: Illustrative search strategy

REPRODUCTIVE GENETIC CARRIER SCREENING			OUTCOME-RELATED TERMS			METHODOLOGICAL TERMS		
Keyword	**#**	**Search Term**	**Keyword**	**#**	**Search Term**	**Keyword**	**#**	**Search Term**
Genetic Carrier Screening	1	Genetic Carrier Screening.mp Genetic Carrier Screening/	Acceptability	1	Acceptability.mp Patient acceptability of health care/	Consensus	1	Consensus*.mp Consensus/ Consensus Development Conference/
Genetic Carrier Testing	2	Genetic Carrier Testing.mp	Attitude	2	Attitude*	Feasibility	2	Feasib*.mp Feasibility studies/
Carrier Screening	3	Carrier Screening.mp	Barrier	3	Barrier*.mp	Focus group	3	Focus group*.mp Focus groups/
Carrier Testing	4	Carrier Testing.mp	Behaviour	4	Behavio*			
Preconception	5	Preconception*.mp	Challenge	5	Challeng*.mp	Implementation	4	Implement*.mp
Expanded	6	Expanded.mp	Clinical utility	6	Clinical utility.mp			
Prenatal	7	Prenatal.mp	Decisional conflict	7	Decisional conflict.mp	Interview	5	Interview*.mp Interview/ Interviews as topic/
Reproductive	8	Reproduct*.mp						
			Decision-making	8	Decision?making.mp Decision Making/	Mixed method	6	Mixed method*.mp
			Experience	9	Experience*.mp	Pilot study	7	Pilot*.mp Pilot Projects/
			Informed consent	10	Informed consent.mp Informed Consent/	Program development or evaluation	8	Program*.mp Program development/ Program evaluation/
			Knowledge	11	Knowledge.mp Health Knowledge, Attitudes, Practice/	Randomised control trial	9	Randomi?sed control* trial*.mp Randomized Controlled Trials as Topic/
			Outcomes	12	Outcome*.mp	Survey/Questionnaire	10	Survey*.mp "Surveys and Questionnaires"/ Health surveys/ Health care surveys/
			Psychosocial	13	Psycho*.mp			
			Patient Satisfaction	14	Patient satisfaction.mp Patient satisfaction/			
			Reproductive behaviour	15	Reproduct* behavio*.mp Reproductive behaviour/	Qualitative	11	Qualitative*.mp Qualitative research/
			Understanding	16	Understand*.mp	Quantitative	12	Quantitative*.mp
			Uptake	17	Uptake.mp			
			Willingness to pay	18	Willingness to pay.mp			
RGCS Search		**(1 or 2 or 3 or 4) AND (5 or 6 or 7 or 8) (2213 articles)**	**Outcomes Search**		**1-18 (OR) (7343415 articles)**	**Methods Search**		**1-12 (OR) (2996983 articles)**

Medline Ovid: "((Genetic Carrier Screening OR Genetic Carrier Testing OR Carrier Screening OR Carrier Testing) AND (Preconception* OR Expanded OR Prenatal OR Reproduct*)) **AND** ((Acceptab* OR Barrier OR Behavio* OR Challeng* OR Clinical Utility OR Decisional Conflict OR Decision?Making OR Experience* OR Informed Consent OR Knowledge OR Outcome* or Psycho* OR Patient Satisfaction OR Reproduct* Behavio* OR Understand* OR Uptake OR Willingness to Pay) **OR** (Consensus* OR Feasib* OR Focus Group* OR Implement* OR Interview* OR Mixed Method* OR Pilot* OR Program* OR Randomi?ed control* trial* OR Survey* OR Qualitative* OR Quantitative*))"

Supplementary material A.2: COMET/CODECS Taxonomy Version 1.0

COMET Core Area	COMET Outcome Domain	CODECS Domain	Definition	Example outcome
Physiological /Clinical	Congenital, familial and genetic outcomes	Primary outcomes of RGCS	Outcomes related to the results of RGCS	- *Carrier detection rate* - *Identification of increased risk couples*
		Secondary or incidental outcomes of RGCS	Outcomes related to laboratory findings not related to the primary indication for screening. This may include findings related to variants of uncertain significance, incidental findings (defined here are as findings that were unexpected), and secondary findings (defined here are secondary outcomes that were deliberately looked for and therefore are not truly incidental)	- *Identification of variants of uncertain significance* - *Identification of homozygous, hemizygous or compound heterozygous individuals at risk for developing one of the screened conditions*
		Other laboratory outcomes	Outcomes related to additional laboratory outcomes other than the primary results	- *Rate of test failure due to insufficient DNA in patient sample* - *Rate of false-positive screening via biochemical analysis*
	Pregnancy, puerperium and perinatal outcomes	Affected births	Outcomes related to new affected cases of the condition being screened	- *Number of affected births despite the screening program* - *Reasons for new affected births*
		Pregnancy outcomes	Outcomes related to the impact of screening results on future pregnancies	- *Results of prenatal diagnosis in future pregnancies* - *Decision to continue or terminate affected foetuses in future pregnancies* - *Results of prenatal diagnosis in pregnancies at the time of screening* - *Decision to continue or terminate an affected fetus in current pregnancy*
Life Impact	Cognitive functioning	Attitudes and perceptions	Outcomes related to patient's attitudes, perceptions or beliefs about RGCS	- *Perception that RGCS would alter reproductive decisions* - *Attitude regarding recommending carrier screening to others*
		Deliberation and informed choice	Outcomes related to making an informed choice to undertake RGCS	- *Deliberation on the decision to accept or decline testing*

				- Informed choice (congruence of attitudes, knowledge and test uptake)
		Knowledge	Outcomes related to knowledge, incorporating concepts of understanding, recall and retention.	*- Understanding of the information received during genetic counselling session* *- Knowledge before and after pre-test genetic counselling*
	Delivery of care	Intention and uptake	Outcomes related to actual or intention to uptake an offer of RGCS	*- Uptake of RGCS* *- Intention to accept the offer of RGCS*
		Barriers and facilitators	Outcomes related to reasons for and against uptake of services including offers of RGCS and further testing	*- Reasons for accepting/declining an offer of RGCS*
		Information sources	Outcomes related to sources of information utilised by patients	*- Sources of additional information used for decision-making regarding uptake of RGCS* *- Sources of information about the carrier screening offer prior to pre-test counselling*
		Genetic counselling	Outcomes related to the use and conduct of genetic counselling services	*- Number of post-test genetic counselling consultations* *- Time required for pre-test genetic counselling session*
		Practice guidelines/recommendations	Outcomes related to clinical practice recommendations	*- Ordering clinicians selection of conditions according to practice recommendations*
		Patient preferences	Outcomes related to patient preferences regarding the offer of RGCS	*- Preference regarding individual or couple-based results*
		Patient satisfaction	Outcomes related to patient satisfaction with services related to RGCS	*- Satisfaction with pre-test genetic counselling*
		Timeliness	Outcomes related to the timeliness of delivery of care in RGCS programs	*- Mean gestational age at time of reproductive carrier screening* *- Offer of reproductive carrier screening to women before 10 weeks gestation*
	Emotional functioning/wellbeing	Decision satisfaction and regret	Outcomes related to decisional satisfaction or regret at a later timepoint	*- Distress or remorse after a healthcare decision measured at a later timepoint* *- Satisfaction with the decision to accept/decline screening*
		Psychological wellbeing	Outcomes related to the psychological impact of RGCS	*- Anxiety (measured at a range of timepoints)* *- Subjective distress associated with being a carrier at a later timepoint*

	Perceived health status	Perception of personal health status after RGCS	Outcomes related to the impact of RGCS on perception of personal health	*- Impact of results on perception of own health*
	Personal circumstances	Decision-making (non-reproductive)	Outcomes related to the impact of results on decisions other than reproductive planning	*- Impact of negative result on decisions related to insurance, healthcare and lifestyle* *- Number of prospective marriages cancelled due to identification as an increased risk couple (pre-marital screening programs)*
		Decision-making (reproductive)	Outcomes related to impact of results on decision-making for reproductive planning, including perceived or actual impact on these decisions	*- Pursued or planned to pursue alternate reproductive options* *- Intended reproductive decisions if identified as a carrier couple*
		Familial implications	Outcomes related to the impact of results of patient relationships	*- Impact of results on couple's relationship* *- Number of carriers that informed family members of their results*
	Social functioning	Privacy concerns and stigmatisation	Outcomes related to the impact of results on privacy and stigmatisation	*- Concern regarding privacy or confidentiality* *- Fear of discrimination of carriers by insurance companies*
Resource Use	Need for further intervention	Further testing	Outcomes related to the use of further testing for various purposes including clarifying reproductive risk as a couple, testing during a pregnancy, or electing PGD	*- Uptake of partner testing* *-Uptake of prenatal diagnosis in increased risk pregnancies at the time of screening* *- Uptake of postnatal diagnostic testing in decliners of prenatal diagnosis in a current pregnancy at the time of screening* *- Uptake of preimplantation genetic diagnosis in increased risk couples*

The development of the CODECS outcome domains was an iterative process, initially compiled at the completion of the quantitative systematic review (Version 1.0 – Appendix A). It was then reviewed and updated at the completion of the qualitative systematic review (Version 1.1 – Appendix B), with the addition of 3 new outcome domains and revisions to the wording of a number of domains and definitions to further clarify and expand on the initial domains. Finally, these were reviewed and revised at the completion of the qualitative interview study (Version 1.2 – Appendix C).

Version 1.0 – original version, defined at completion of the quantitative systematic review and consisting of 24 CODECS domains

Supplementary material A.3: Summary of included studies

Study ID	Author and Year	Publication Title	Country	Test Type	Study Design	Number of Outcomes Reported
1	Archibald et al. 2018 [1]	Reproductive genetic carrier screening for cystic fibrosis, fragile X syndrome and spinal muscular atrophy in Australia: Outcomes of 12,000 tests	Australia	3-gene (CF, FXS, SMA)	Descriptive cross-sectional study, retrospective	14
2.1	Ioannou et al. 2010 [2]	Evaluation of a multi-disease carrier screening program in Ashkenazi Jewish high schools	Australia	Targeted Panel in Founder Population	Analytic cohort study, prospective	8
2.2	Curd et al. 2014 [3]	High school Tay-Sachs disease carrier screening: 5 to 11-year follow-up	Australia	Targeted Panel in Founder Population	Analytic cohort study, prospective	10
3.1	Ioannou et al. 2010 [4]	Population-based genetic screening for cystic fibrosis: attitudes and outcomes	Australia	CF	Analytic cross-sectional study, retrospective	7
3.2	Ioannou et al. 2014 [5]	'No thanks'—reasons why pregnant women declined an offer of cystic fibrosis carrier screening	Australia	CF	Analytic cross-sectional study, retrospective	7
4	Lew et al. 2012 [6]	Tay Sachs disease in Australia: reduced disease incidence despite stable carrier frequency in Australian Jews	Australia	Targeted Panel in Founder Population	Descriptive cross-sectional study, retrospective	2
5	Metcalfe et al. 2017 [7]	Offering fragile X syndrome carrier screening: a prospective mixed-methods observational study comparing carrier screening of pregnant and non-pregnant women in the general population	Australia	FXS	Analytic cohort study, prospective	12
6	Robson et al. 2020 [8]	Socioeconomic status and uptake of reproductive carrier screening in Australia	Australia	3-gene (CF, FXS, SMA) or ECS	Analytic cross-sectional study, retrospective	2
7.1	Liao et al. 2015 [9]	Prenatal control of Hb Bart's hydrops fetalis: a two-year experience at a mainland Chinese hospital	China	Haemoglobinopathies	Descriptive cross-sectional study, prospective	4
7.2	Jiang et al. 2017 [10]	Pre-gestational thalassemia screening in mainland China: the first two years of a preventive program	China	Haemoglobinopathies	Descriptive cross-sectional study, prospective	9

8	Zhang et al. 2020 [11]	Carrier screening and prenatal diagnosis for spinal muscular atrophy in 13,069 Chinese pregnant women	China	SMA	Descriptive cross-sectional study, prospective	11
9	Ladis et al. 2013 [12]	Thirty-year experience in preventing haemoglobinopathies in Greece: achievements and potentials for optimisation.	Greece	Haemoglobinopathies	Analytic cross-sectional study, retrospective	2
10	Theodoridou et al. 2018 [13]	Efficacy of the national thalassaemia and sickle cell disease prevention programme in Northern Greece: 15-year experience, practice and policy gaps for natives and migrants	Greece	Haemoglobinopathies	Descriptive cross-sectional study, retrospective	10
11	Baxi et al. 2013 [14]	Carrier screening for beta thalassemia in pregnant Indian Women: Experience at a single centre in Madhya Pradesh	India	Haemoglobinopathies	Descriptive cross-sectional study, prospective	8
12	Ghosh et al. 2019 [15]	Thalassaemia carrier detection during antenatal period: Single centre experience from Eastern India	India	Haemoglobinopathies	Descriptive cross-sectional study, prospective	2
13.1	Ben-Shachar et al. 2011 [16]	Large-scale population screening for spinal muscular atrophy: Clinical implications	Israel	SMA	Descriptive cross-sectional study, prospective	9
13.2	Aharoni et al. 2020 [17]	Impact of a national population-based carrier-screening program on spinal muscular atrophy births	Israel	SMA	Descriptive cross-sectional study, retrospective	6
14	Macarov et al. 2011 [18]	Genetic screening for Krabbe disease: Learning from the past and looking to the future	Israel	Targeted Panel in Founder Population	Descriptive cross-sectional study, retrospective	8
15	Singer et al. 2020 [19]	Impact of a national genetic carrier-screening program for reproductive purposes	Israel	Targeted Panel in Founder Population	Descriptive cross-sectional study, retrospective	7
16	Amato et al. 2014 [20]	Carrier screening for inherited haemoglobin disorders among secondary school students and young adults in Latium, Italy	Italy	Haemoglobinopathies	Descriptive cross-sectional study, retrospective	5
17	Castellani et al. 2016 [21]	Cystic fibrosis carrier screening effects on birth prevalence and newborn screening	Italy	CF	Analytic cohort study, retrospective	6

18	Coiana et al. 2011 [22]	Preconceptional identification of cystic fibrosis carriers in the Sardinian population: A pilot screening program	Italy	CF	Descriptive cross-sectional study, prospective	7
19	Giambona et al. 2015 [23]	Incidence of haemoglobinopathies in Sicily: The impact of screening and prenatal diagnosis	Italy	Haemoglobinopathies	Descriptive cross-sectional study, retrospective	13
20	Monni et al. 2018 [24]	From Prenatal to Preimplantation Genetic Diagnosis of β-Thalassemia. Prevention Model in 8748 Cases: 40 Years of Single Center Experience	Italy	Haemoglobinopathies	Descriptive cross-sectional study, retrospective	10
21	Picci et al. 2010 [25]	A 10-year large-scale cystic fibrosis carrier screening in the Italian population	Italy	CF	Descriptive cross-sectional study, retrospective	6
22	Kim et al. 2013 [26]	Fragile X carrier screening in Korean women of reproductive age	Korea	FXS	Descriptive cross-sectional study, retrospective	5
23	Abi Saad et al. 2014 [27]	Preventing thalassemia in Lebanon: Successes and challenges in a developing country	Lebanon	Haemoglobinopathies	Descriptive cross-sectional study, retrospective	3
24	Su et al. 2011 [28]	Carrier screening for spinal muscular atrophy (SMA) in 107,611 pregnant women during the period 2005-2009: a prospective population-based cohort study	Taiwan	SMA	Descriptive cross-sectional study, prospective	9
25	Tzeng et al. 2017 [29]	A 15-year-long Southern blotting analysis of FMR1 to detect female carriers and for prenatal diagnosis of fragile X syndrome in Taiwan	Taiwan	FXS	Descriptive cross-sectional study, retrospective	3
26	Tongsong et al. 2013 [30]	Effectiveness of the model for prenatal control of severe thalassemia	Thailand	Haemoglobinopathies	Descriptive cross-sectional study, prospective	8
27	Yamsri et al. 2010 [31]	Prevention of severe thalassemia in northeast Thailand: 16 years of experience at a single university center	Thailand	Haemoglobinopathies	Descriptive cross-sectional study, retrospective	6
28	Kaufmann et al. 2011 [32]	Feasibility of nonselective testing for hemoglobinopathies in early pregnancy in The Netherlands.	The Netherlands	Haemoglobinopathies	Descriptive cross-sectional study, prospective	12

29.1	Mathijssen et al. 2015 [33]	Targeted carrier screening for four recessive disorders: High detection rate within a founder population	The Netherlands	Targeted Panel in Founder Population	Descriptive cohort study, prospective	6
29.2	Mathijssen et al. 2018 [34]	Preconception carrier screening for multiple disorders: evaluation of a screening offer in a Dutch founder population	The Netherlands	Targeted Panel in Founder Population	Descriptive cohort study, prospective	23
30.1	Schuurmans et al. 2019 [35]	Feasibility of couple-based expanded carrier screening offered by general practitioners	The Netherlands	ECS	Descriptive cohort study, prospective	7
30.2	Schuurmans et al. 2019 [36]	GP-provided couple-based expanded preconception carrier screening in the Dutch general population: who accepts the test-offer and why?	The Netherlands	ECS	Descriptive cohort study, prospective	6
31	Canatan et al. 2016 [37]	Report on ten years' experience of premarital hemoglobinopathy screening at a centre in Antalya, Southern Turkey	Turkey	Haemoglobinopathies	Descriptive cross-sectional study, retrospective	4
32	Guler et al. 2010 [38]	Premarital screening results for β Thalassemia and sickle cell anaemia trait in east Mediterranean region of Turkey	Turkey	Haemoglobinopathies	Descriptive cross-sectional study, retrospective	5
33	Belhoul et al. 2013 [39]	Hemoglobinopathy carrier prevalence in the United Arab Emirates: First analysis of the Dubai health authority premarital screening program results	UAE	Haemoglobinopathies	Descriptive cross-sectional study, retrospective	5
34.1	Dormandy et al. 2010 [40]	Effectiveness of earlier antenatal screening for sickle cell disease and thalassaemia in primary care: cluster randomised trial	UK	Haemoglobinopathies	Randomised controlled trial, cluster randomised	7
34.2	Brown et al. 2011 [41]	Impact on informed choice of offering antenatal sickle cell and thalassaemia screening in primary care: a randomised trial	UK	Haemoglobinopathies	Randomised controlled trial, cluster randomised	4
34.3	Dormandy et al. 2010 [42]	Antenatal screening for haemoglobinopathies in primary care: a cohort study and cluster randomised trial to inform a simulation model. The Screening for Haemoglobinopathies in First Trimester (SHIFT) trial	UK	Haemoglobinopathies	Randomised controlled trial, cluster randomised	16

35.1	Scott et al. 2010 [43]	Experience with carrier screening and prenatal diagnosis for 16 Ashkenazi Jewish genetic diseases	USA	Targeted Panel in Founder Population	Descriptive cross-sectional study, retrospective	5
35.2	Akler et al. 2020 [44]	Lessons learned from expanded reproductive carrier screening in self-reported Ashkenazi, Sephardi, and Mizrahi Jewish patients	USA	Targeted Panel in Founder Population	Descriptive cross-sectional study, retrospective	6
36	Carlotti et al. 2020 [45]	Perceived barriers to paternal expanded carrier screening following a positive maternal result: To screen or not to screen	USA	ECS	Analytic cross-sectional study, retrospective	4
37.1	Gilmore et al. 2017 [46]	Reasons for declining preconception expanded carrier screening using genome sequencing	USA	ECS	Randomised controlled trial	2
37.2	Clarke et al. 2018 [47]	Assessment of willingness to pay for expanded carrier screening among women and couples undergoing preconception carrier screening	USA	ECS	Randomised controlled trial	1
37.3	Kraft et al. 2018 [48]	Patient actions and reactions after receiving negative results from expanded carrier screening	USA	ECS	Randomised controlled trial	11
37.4	Punj et al. 2018 [49]	Preconception carrier screening by genome sequencing: Results from the clinical laboratory	USA	ECS	Randomised controlled trial	6
38.1	Lazarin et al. 2013 [50]	An empirical estimate of carrier frequencies for 400+ causal Mendelian variants: results from an ethnically diverse clinical sample of 23,453 individuals.	USA	ECS	Analytic cohort study, retrospective	3
38.2	Ghiossi et al. 2018 [51]	Clinical utility of expanded carrier screening: Reproductive behaviours of at-risk couples	USA	ECS	Analytic cohort study, retrospective	6
38.3	Johansen Taber et al. 2019 [52]	Clinical utility of expanded carrier screening: results-guided actionability and outcomes	USA	ECS	Analytic cohort study, retrospective	9
38.4	Johansen Taber et al. 2019 [53]	Fragile X syndrome carrier screening accompanied by genetic consultation has clinical utility in populations beyond those recommended by guidelines	USA	FXS	Analytic cohort study, retrospective	10

39	Giles Choates et al. 2020 [54]	It takes two: uptake of carrier screening among male reproductive partners	USA	ECS	Analytic cross-sectional study, retrospective	10
40.1	Grinzaid et al. 2015 [55]	Creation of a national, at-home model for Ashkenazi Jewish carrier screening	USA	Targeted Panel in Founder Population	Descriptive cross-sectional study, prospective	8
40.2	Hardy et al. 2018 [56]	Implementation of a carrier screening program in a high-risk undergraduate student population using digital marketing, online education, and telehealth	USA	Targeted Panel in Founder Population	Descriptive cross-sectional study, prospective	7
40.3	Yip et al. 2019 [57]	Patients' reactions and follow-up testing decisions related to Tay-Sachs (HEXA) variants of uncertain significance results	USA	Targeted Panel in Founder Population	Analytic cross-sectional study, retrospective	7
41	Kuhl et al. 2016 [58]	Development of carrier testing for common inborn errors of metabolism in the Wisconsin Plain population	USA	Targeted Panel in Founder Population	Descriptive cross-sectional study, prospective	3
42	Larsen et al. 2019 [59]	The uptake of pan-ethnic expanded carrier screening is higher when offered during preconception or early prenatal genetic counseling	USA	ECS	Analytic cross-sectional study, retrospective	2
43	Prior et al. 2010 [60]	Newborn and carrier screening for spinal muscular atrophy	USA	SMA	Descriptive cross-sectional study, prospective	11
44	Propst et al. 2018 [61]	Pregnant women's perspectives on expanded carrier screening	USA	ECS	Descriptive cross-sectional study, prospective	4
45	Shao et al. 2015 [62]	Evaluation of two-year Jewish genetic disease screening program in Atlanta: insight into community genetic screening approaches	USA	Targeted Panel in Founder Population	Descriptive cross-sectional study, retrospective	6
46	Simone et al. 2020 [63]	Reproductive male partner testing when the female is identified to be a genetic disease carrier	USA	ECS	Analytic cross-sectional study, retrospective	5

47	Warsch et al. 2014 [64]	Knowledge, attitudes, and barriers to carrier screening for the Ashkenazi Jewish panel: a Florida experience	USA	Targeted Panel in Founder Population	Descriptive cross-sectional study, prospective	9
48	Westemeyer et al. 2020 [65]	Clinical experience with carrier screening in a general population: support for a comprehensive pan-ethnic approach	USA	ECS	Descriptive cross-sectional study, retrospective	3

Supplementary material A.4: Risk of bias assessment

Higher scores represent higher quality and less risk of bias (scale of 0-1)

First Author and Year	QualSyst Score
Abi Saad (2014)[27]	0.57
Aharoni (2020)[73]	0.71
Akler (2020)[44]	0.93
Amato (2014)[20]	0.50
Archibald (2018)[1]	1.00
Baxi (2013)[14]	0.71
Belhoul (2013)[39]	0.86
Ben-Shachar (2011)[16]	0.79
Brown (2011)[41]	1.00
Canatan (2016)[37]	0.57
Carlotti (2020)[74]	0.82
Castellani (2016)[21]	0.86
Clarke (2018)[47]	0.95
Coiana (2011)[22]	0.79
Curd (2014)[3]	1.00
Dormandy (2010)[40]	1.00
Dormandy (2010)_2[42]	1.00
Ghiossi (2018)[75]	0.86
Ghosh (2019)[76]	0.73
Giambona (2015)[23]	0.64
Giles Choates (2020)[54]	0.73
Gilmore (2017)[46]	0.95
Grinzaid (2015)[55]	0.57
Guler (2010)[38]	0.50
Hardy (2018)[56]	1.00
Ioannou (2010)_1[4]	1.00
Ioannou (2010)_2[2]	1.00
Ioannou (2014)[5]	1.00
Jiang (2017)[10]	0.86
Johansen Taber (2019)[53]	0.86
Johansen Taber (2019)_2[52]	0.86
Kaufmann (2011)[32]	0.93
Kim (2013)[26]	0.86

First Author and Year	QualSyst Score
Kraft (2018)[48]	0.92
Kuhl (2016)[58]	0.71
Ladis (2013)[12]	0.77
Larsen (2019)[59]	0.95
Lazarin (2013)[50]	0.93
Lew (2012)[66]	0.86
Liao (2015)[9]	0.64
Macarov (2011)[18]	0.71
Mathijssen (2015)[67]	0.93
Mathijssen (2018)[34]	1.00
Metcalfe (2017)[7]	1.00
Monni (2018)[24]	0.79
Picci (2010)[25]	0.93
Prior (2010)[60]	0.71
Propst (2018)[61]	0.93
Punj (2018)[49]	0.93
Robson (2020)[68]	0.77
Schuurmans (2019)_1[69]	0.93
Schuurmans (2019)_2[36]	0.79
Scott (2010)[43]	0.79
Shao (2015)[62]	0.86
Simone (2020)[70]	0.95
Singer (2019)[71]	0.71
Su (2011)[28]	1.00
Theodoridou (2018)[13]	0.93
Tongsong (2013)[30]	0.86
Tzeng (2017)[29]	0.71
Warsch (2014)[64]	0.86
Westemeyer (2020)[72]	0.64
Yamsri (2010)[31]	0.86
Yip (2019)[57]	0.61
Zhang (2020)[11]	0.43

Supplementary material A.5: List of outcomes extracted from quantitative studies

COMET Core Area	COMET Domains	CODECS Domains	ID	Outcome Description
Physiological and clinical outcomes	Congenital, familial, and genetic outcomes	Primary outcomes of RGCS	1	Carrier detection rate from biochemical analysis
			2	Carrier detection rate from DNA analysis
			3	Identification of increased risk couples
		Secondary or incidental outcomes of RGCS	4	Identification of medically actionable secondary findings
			5	Identification of variants associated with milder presentations
			6	Identification of variants of uncertain significance
			7	Incidental identification of clinically significant CNV
			8	Incidental identification of homozygous, hemizygous or compound heterozygous individuals
			9	Incidental identification of suspected triple X syndrome in maternal sample
			10	Rate of non-paternity revealed through prenatal diagnosis
		Other laboratory outcomes	11	Molecular confirmations (e.g. homozygotes indicated from biochemical assay, or obligate carriers)
			12	Outcomes from ancillary or alternative methods to DNA analysis
			13	Rate of test failure (e.g. due to insufficient DNA)
			14	Laboratory errors
	Pregnancy, puerperium, and perinatal outcomes	Affected births	15	Number of affected births
			16	Reasons for cases of new affected births
		Pregnancy outcomes	17	Decision to continue or terminate a pregnancy identified as affected through prenatal diagnosis
			18	Rate of fetal loss following prenatal diagnosis
			19	Results of preimplantation genetic diagnosis and pregnancy outcomes
			20	Results of prenatal diagnoses

COMET Core Area	COMET Domains	CODECS Domains	ID	Outcome Description
Life impact	Cognitive functioning	Attitudes and perceptions	21	Attitude regarding sharing genetic test results with family or partner
			22	Attitude towards RGCS
			23	Attitudes regarding recommending carrier screening to others
			24	Attitudes, feelings and beliefs about expanded carrier screening
			25	Belief that carrier screening should be available to those who wish to have it
	Cognitive functioning	Attitudes and perceptions	26	Perceived risk of being a carrier
			27	Perception that RGCS would influence reproductive choices
		Deliberation and informed choice	28	Deliberation - the extent to which a decision to accept or decline testing is deliberated on
			29	Deliberation - the extent to which the decision to accept pre-test genetic counselling was considered
			30	Informed choice (congruence of knowledge, attitudes and test uptake)
		Knowledge and understanding	31	Awareness of the condition(s) tested prior to the screening offer
			32	Correct understanding of the purpose of testing and implications of results
			33	Recall of correct screening result at a later timepoint
			34	Retention of knowledge about the condition(s) tested over time
			35	Understanding of the information received during genetic counselling session
	Emotional functioning and wellbeing	Psychological wellbeing	36	Anxiety
			37	Concern regarding anxiety that will be caused by carrier screening before and after education
			38	Concern/reassurance for baby's health
			39	Depression
			40	Feelings about the test result
			41	Perceived ability to cope with results

COMET Core Area	COMET Domains	CODECS Domains	ID	Outcome Description
Life impact (continued)	Emotional functioning and wellbeing (continued)	Psychological wellbeing (continued)	42	Predicted negative feelings if found to be a carrier
			43	Stress at two timepoints (Q1 after making a decision about carrier screening, Q2 one month after Q1)
			44	Subjective distress associated with being a carrier at a later timepoint
			45	Worry about test results measured 3 months after results
		Decision satisfaction and regret	46	Decisional conflict pertaining to undertaking further testing to clarify carrier status
			47	Patient attitude that they would make the same decision to accept RGCS again
			48	Decision regret – distress or remorse after a healthcare decision measured at a later timepoint
			49	Gladness – retrospective satisfaction with decision to have reproductive carrier screening
			50	Retrospective appraisal of the decision to undergo screening
			51	Satisfaction with decision to decline screening
			52	Satisfaction with the decision to accept screening
	Social functioning	Privacy concerns and stigmatisation	53	Concern regarding privacy or confidentiality
			54	Fear of discrimination of carriers by insurance companies
			55	Impact of carrier screening on stigmatization
	Delivery of care	Barriers and facilitators	56	Reasons or factors influencing uptake of partner testing
			57	Reasons or factors influencing acceptance of pre-test counselling
			58	Reasons or factors influencing uptake of further testing to clarify a VUS
			59	Reasons or factors influencing uptake of RGCS
			60	Reasons or factors influencing pursued or planned reproductive decisions in increased risk couples
			61	Reasons or factors influencing pursued or planned uptake of postnatal diagnosis
			62	Reasons or factors influencing uptake of prenatal diagnosis

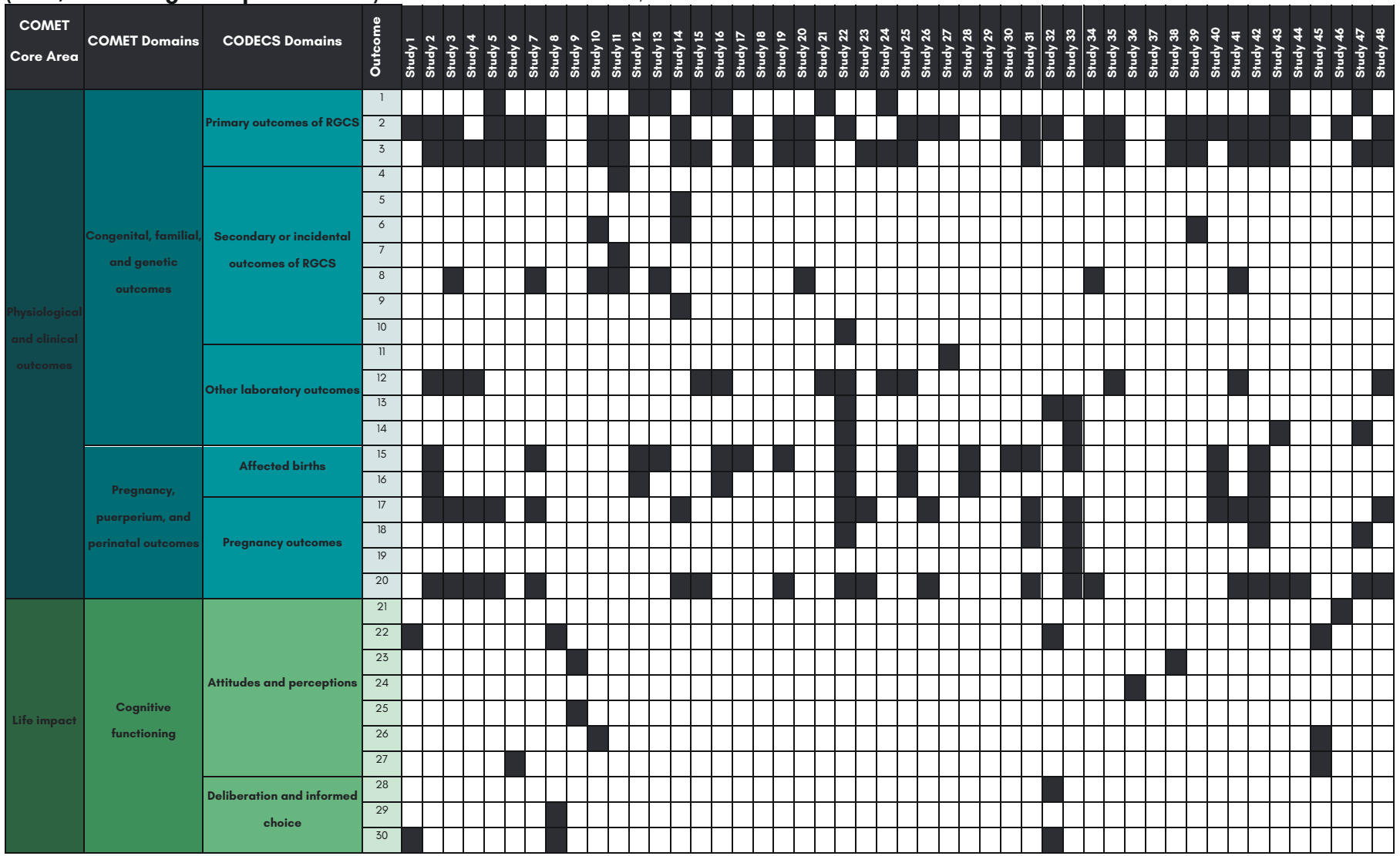
COMET Core Area	COMET Domains	CODECS Domains	ID	Outcome Description
Life impact (continued)	**Delivery of care (continued)**	**Information sources**	63	Sources of additional information used to make a decision regarding uptake of carrier screening
			64	Sources of information about the carrier test offer
			65	Sources of information about the condition(s) tested prior to the screening offer
		Genetic counselling	66	Mode of post-test genetic counselling for carriers identified through RGCS
			67	Number of post-test genetic counselling consultations
			68	Recall of receiving educational material prior to electing screening
			69	Time required for pre-test genetic counselling session
			70	Uptake of pre-test genetic counselling to find out about RCS
			71	Median number of days between receiving results and follow-up genetic counselling
		Intention and uptake	72	Decline of an offer of reproductive carrier screening
			73	Intention to accept the RGCS test offer
			74	Number of screening tests conducted
			75	Uptake of RGCS
			76	Willingness to pay for expanded carrier screening
		Patient preferences	77	Attitudes regarding dissemination of results to primary care physicians
			78	Opinion regarding timing and setting of reproductive carrier screening
			79	Preference for expanded panel over targeted screening based on ethnicity
			80	Preference for which conditions are included in screening
			81	Preference regarding genetic counselling and preferred provider
			82	Preference regarding individual or couple-based results

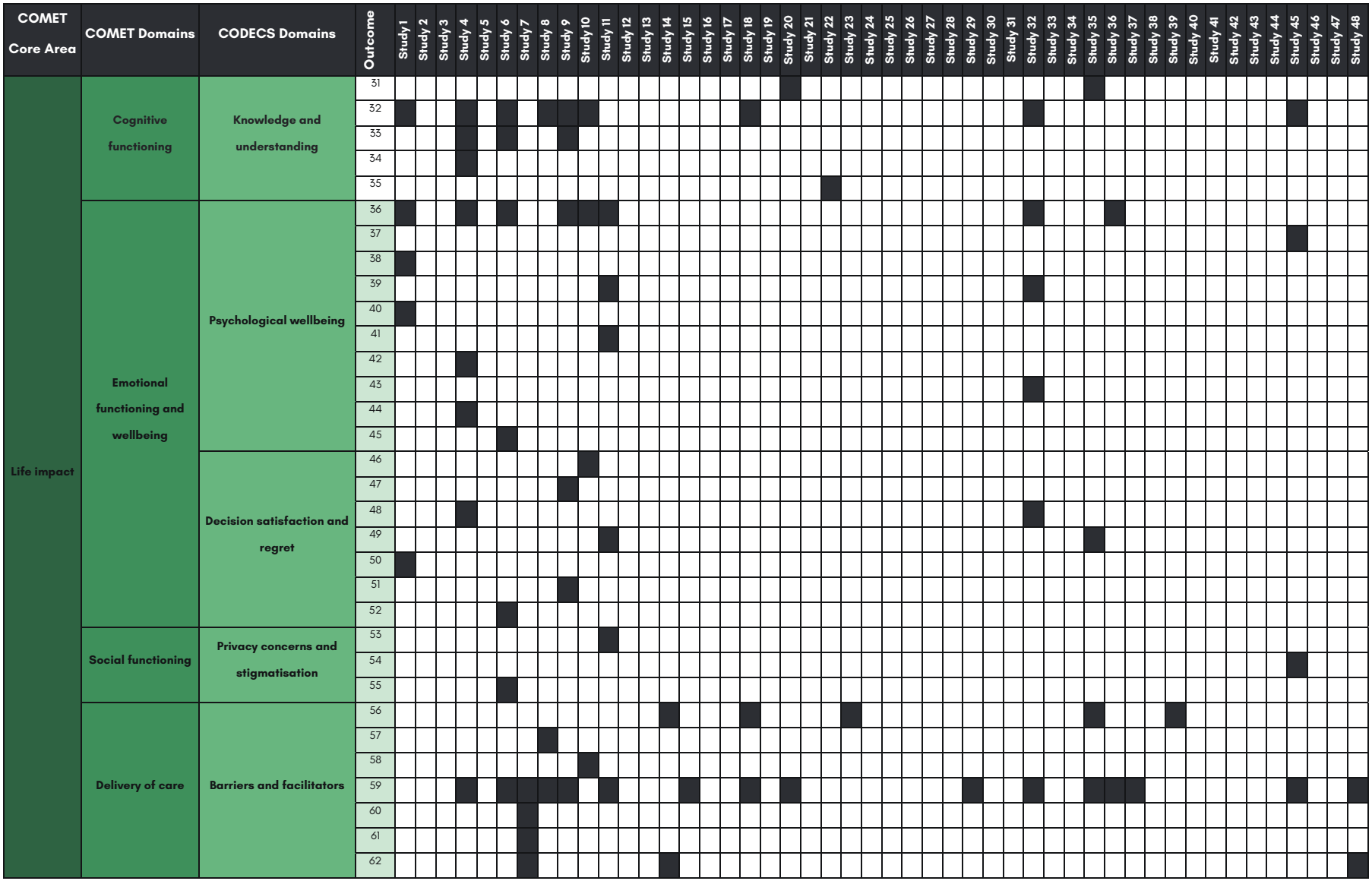
COMET Core Area	COMET Domains	CODECS Domains	ID	Outcome Description
Life impact (continued)	**Delivery of care (continued)**	**Patient satisfaction**	83	Attitude regarding the helpfulness of the educational material provided
			84	Desire for additional information before and after screening
			85	Number of participants that felt they had enough information to decide to accept screening
			86	Satisfaction with pre-test genetic counselling
			87	Satisfaction with the screening process
			88	Worry about accuracy of test results
			89	Satisfaction with timing and setting of reproductive carrier screening
		Practice guidelines and recommendations	90	Ordering clinician's selection of conditions according to practice recommendations
			91	Patient reason for screening corresponds to practice guidelines for that condition
			92	Carriers that would have been missed by small or ethnicity-specific panels
		Timeliness	93	Time between presentation at GP and screening
			94	Gestational age at prenatal diagnosis
			95	Time between maternal results and partner results
			96	Gestational age at time of partners results
			97	Gestational age when offered screening
			98	Proportion of women screened before 10 weeks gestation
			99	Proportion of women screened before 12 weeks gestation
			100	Proportion of women screened before 16 weeks gestation
			101	Proportion of women screened by 26 weeks gestation
			102	Turnaround time for results
			103	Gestational age at the time of RGCS

COMET Core Area	COMET Domains	CODECS Domains	ID	Outcome Description
Life impact (continued)	**Personal circumstances**	**Decision-making (non-reproductive)**	104	Impact of negative result on decisions related to insurance, healthcare and lifestyle
			105	Number of prospective marriages cancelled due to identification as an increased risk couple
		Decision-making (reproductive)	106	Impact of results on reproductive decisions
			107	Decision to refrain from having more children in carrier couples who already have children
			108	Impact of negative result on family planning
			109	Intended reproductive decisions if identified as a carrier couple
			110	Pursued or planned to pursue alternate reproductive options
		Familial implications	111	Concern about implications of results for family members
			112	Impact of results on couple's relationship
			113	Number of carriers that informed family members of their results
	Perceived health status	**Perception of personal health**	114	Impact of results on perception of own health
Resource use	**Need for intervention**	**Further testing**	115	Uptake of partner testing
			116	Uptake of NIPS for sex determination prior to considering invasive prenatal diagnosis
			117	Uptake of postnatal diagnostic testing in decliners of prenatal diagnosis
			118	Uptake of prenatal diagnosis in increased risk pregnancies at the time of screening
			119	Uptake of preimplantation genetic diagnosis in increased risk couples
			120	Mean rate of prenatal diagnosis since implementation of RGCS program

Supplementary material A.6: Block diagram of outcomes reported per study

(n=48; consisting of 65 publications) Outcome IDs from Table 5, studies listed in footnotes




COMET Core Area
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CODECS Domains
Outcome
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Study 12
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Study 34
Study 35
Study 36
Study 37
Study 38
Study 39
Study 40
Study 41
Study 42
Study 43
Study 44
Study 45
Study 46
Study 47
Study 48
Life impact
Cognitive functioning
Knowledge and understanding
31
32
33
34
35
Emotional functioning and wellbeing
Psychological wellbeing
36
37
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43
44
45
Decision satisfaction and regret
46
47
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49
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Social functioning
Privacy concerns and stigmatisation
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Delivery of care
Barriers and facilitators
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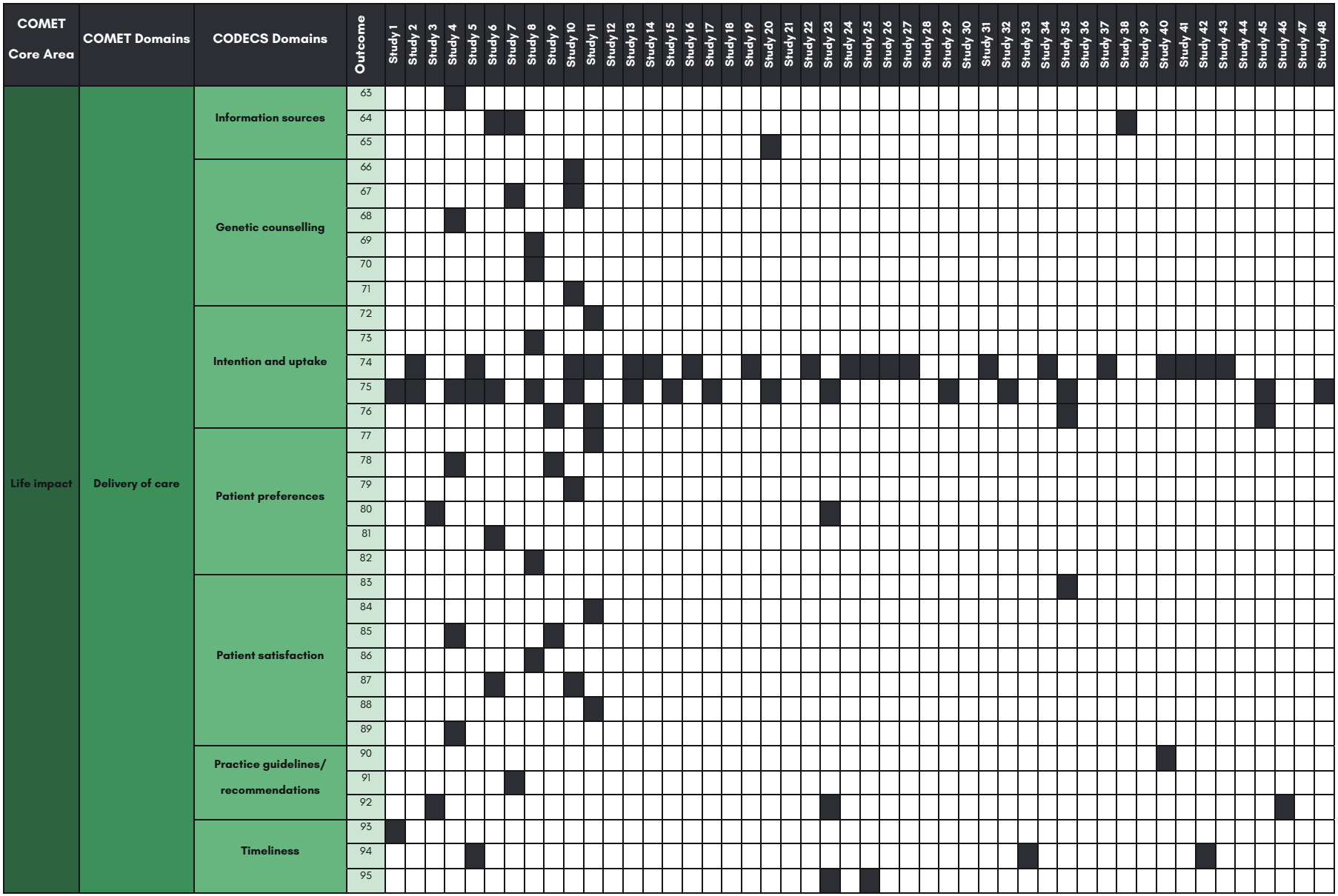
COMET Core Area
COMET Domains
CODECS Domains
Outcome
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Study 47
Study 48
Life impact
Delivery of care
Information sources
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Genetic counselling
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Intention and uptake
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Patient preferences
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Patient satisfaction
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Practice guidelines/ recommendations
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Timeliness
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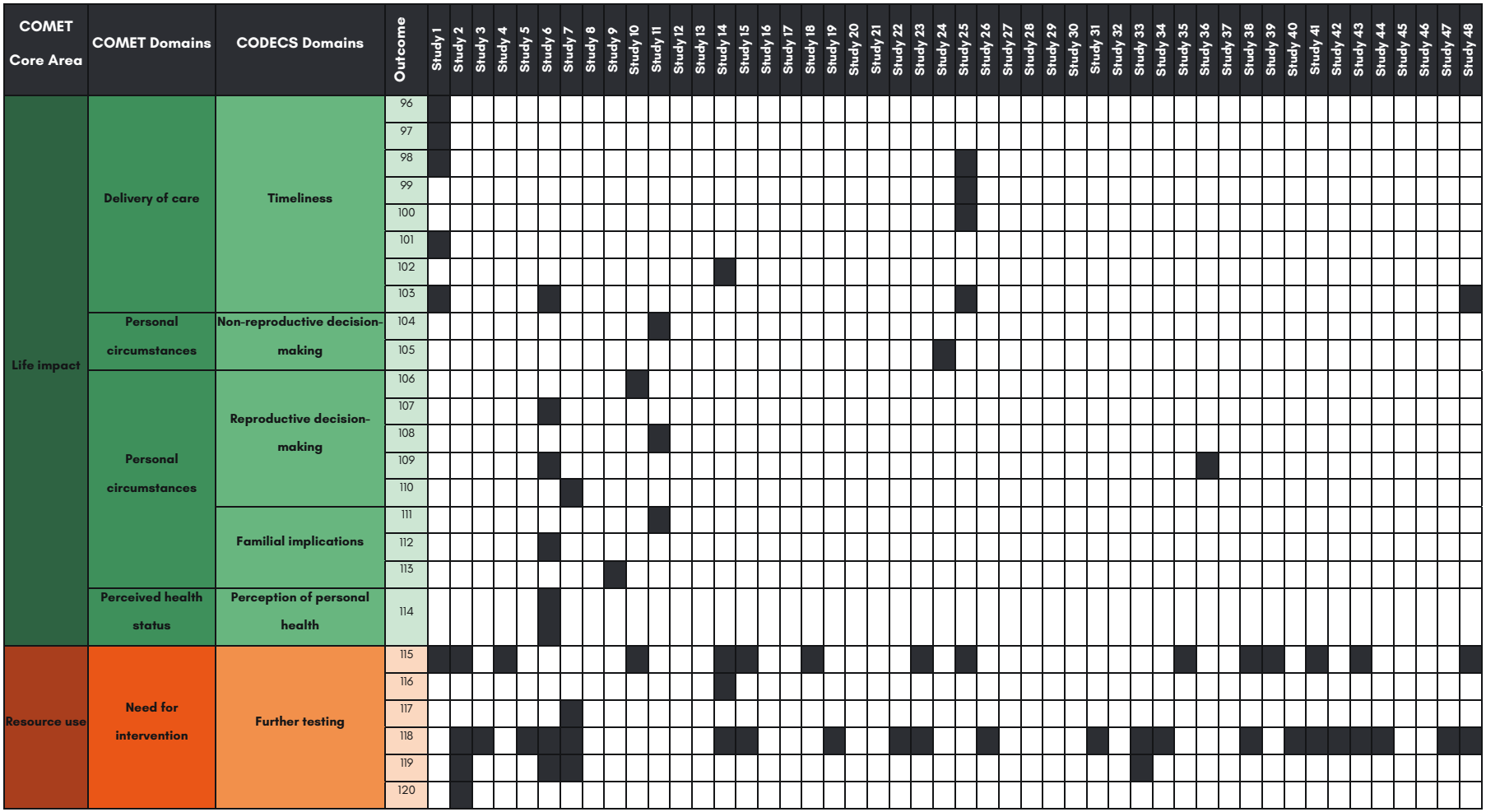

Study 1 – *Brown (2011)[41]; Dormandy (2010)[49]; Dormandy (2010)[48];* **Study 2** – *Aharoni (2020)[34]; Ben-Shachar (2011)[40];* **Study 3** – *Akler (2020)[35]; Scott (2010)[20];* **Study 4** – *Curd (2014)[47]; Ioannou (2010)[59];* **Study 5** – *Liao (2015)[7]; Jiang (2017)[61];* **Study 6** – *Mathijssen (2015)[9]; Mathijssen (2018)[10];* **Study 7** – *Johansen Taber (2019)[62]; Johansen-Taber (2019)[63]; Ghiossi (2018)[50]; Lazarin (2013)[5];* **Study 8** – *Schuurmans (2019)[18]; Schuurmans (2019)[19];* **Study 9** – *Ioannou (2010)[58]; Ioannou (2014)[60];* **Study 10** – *Grinzaid (2015)[55]; Hardy (2018)[57]; Yip (2019)[31];* **Study 11** – *Clarke (2018)[45]; Gilmore (2017)[54]; Kraft (2018)[1]; Punj (2018)[16];* **Study 12** – *Abi Saad (2014)[33];* **Study 13** – *Amato (2014)[36];* **Study 14** – *Archibald (2018)[37];* **Study 15** – *Baxi (2013)[38];* **Study 16** – *Belhoul (2013)[39];* **Study 17** – *Canatan (2016)[42];* **Study 18** – *Carlotti (2020)[43];* **Study 19** – *Castellani (2016)[44];* **Study 20** – *Coiana (2011)[46];* **Study 21** – *Ghosh (2019)[51];* **Study 22** – *Giambona (2015)[52];* **Study 23** – *Giles Choate (2020)[53];* **Study 24** – *Guler (2010)[56];* **Study 25** – *Kaufmann (2011)[64];* **Study 26** – *Kim (2013)[65];* **Study 27** – *Kuhl (2016)[2];* **Study 28** – *Ladis (2013)[5];* **Study 29** – *Larsen (2019)[4];* **Study 30** – *Lew (2012)[6];* **Study 31** – *Macarov (2011)[8];* **Study 32** – *Metcalfe (2017)[11];* **Study 33** – *Monni (2018)[12];* **Study 34** – *Picci (2010)[13];* **Study 35** – *Prior (2010)[14];* **Study 36** – *Propst (2018)[15];* **Study 37** – *Robson (2020)[17];* **Study 38** – *Shao (2015)[21];* **Study 39** – *Simone (2020)[22];* **Study 40** – *Singer (2020)[23];* **Study 41** – *Su (2011)[24];* **Study 42** – *Theodoridou (2018)[25];* **Study 43** – *Tongsong (2013)[26];* **Study 44** – *Tzeng (2017)[27];* **Study 45** – *Warsch (2014)[28];* **Study 46** – *Westemeyer (2020)[29];* **Study 47** – *Yamsri (2010)[30];* **Study 48** – *Zhang (2020)[32]*

Supplementary material A.7: Outcome measurement methods

Outcomes measured using a previously reported or validated measurement tool.

CODECS Outcome Domain	Outcome	Measurement Methods	Previously Reported/Validated Measurement Tools
Psychological wellbeing	Anxiety	Validated or previously reported scale	Depression Anxiety Stress Scale (DASS-21)[78] State Trait Anxiety Index (STAI-6)[79] Impact of Events Scale[80]
	Depression	Validated or previously reported scale	Depression Anxiety Stress Scale (DASS-21)[78] Patient Health Questionnaire-8 (PHQ-8)[81]
	Feelings about the test result	Validated or previously reported scale	Non-validated scale from another study[82]
	Stress at two timepoints (Q1 after making a decision about carrier screening, Q2 one month after Q1)	Validated or previously reported scale	Depression Anxiety Stress Scale (DASS-21)[78]
	Subjective distress associated with being a carrier at a later timepoint	Validated or previously reported scale	Impact of Events Scale[80]
Deliberation and informed choice	Attitude towards RGCS	Mix (validated and investigator-derived)	Multidimensional measure of informed choice (MMIC)[83] Multidimensional measure of informed choice (MMIC) validated in low literacy population[84]
	Deliberation - the extent to which a decision to accept or decline testing is deliberated on	Validated or previously reported scale	Measure of informed decision-making[85]
	Informed choice (congruence of knowledge, attitudes and test uptake)	Validated or previously reported scale	Multidimensional measure of informed choice (MMIC)[83] Multidimensional measure of informed choice (MMIC) validated in low literacy population[84]

Decision satisfaction or regret	Decision regret – distress or remorse after a healthcare decision measured at a later timepoint	Validated or previously reported scale	Decision regret scale[86]
	Decisional conflict pertaining to undertaking further testing to clarify carrier status	Validated or previously reported scale	Decisional conflict scale[87]
	Satisfaction with decision to decline screening	Validated or previously reported scale	Decision regret scale[86]
	Retrospective appraisal of the decision to undergo screening	Validated or previously reported scale	Decisional conflict scale[87]
Knowledge	Knowledge of RGCS and included conditions	Mix (validated and investigator-derived)	Fragile X syndrome (FXS) knowledge scale[88] Adapted version of validated scale[89] Adapted knowledge section of the MMIC[90] Adapted version of previously published knowledge scale, piloted before use[91] Adapted knowledge scale previously developed by the same research group and used in a variety of studies, piloted before use[92-95] Adapted knowledge scale, loosely based on previously reported scales[82,96]
	Retention of knowledge about the condition(s) tested over time	Validated or previously reported scale	Adapted version of validated scale[89]

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Appendix B – Supporting information for Chapter 4

Summary of Content

Supplementary material B.1 – Illustrative search strategy

Supplementary material B.2 – COMET/CODECS taxonomy version 1.1

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Supplementary material B.1: Illustrative search strategy

REPRODUCTIVE GENETIC CARRIER SCREENING			OUTCOME-RELATED TERMS			METHODOLOGICAL TERMS		
Keyword	**#**	**Search Term**	**Keyword**	**#**	**Search Term**	**Keyword**	**#**	**Search Term**
Genetic Carrier Screening	1	Genetic Carrier Screening.mp Genetic Carrier Screening/	Acceptability	1	Acceptability.mp Patient acceptability of health care/	Consensus	1	Consensus*.mp Consensus/ Consensus Development Conference/
Genetic Carrier Testing	2	Genetic Carrier Testing.mp	Attitude	2	Attitude*	Feasibility	2	Feasib*.mp Feasibility studies/
Carrier Screening	3	Carrier Screening.mp	Barrier	3	Barrier*.mp	Focus group	3	Focus group*.mp Focus groups/
Carrier Testing	4	Carrier Testing.mp	Behaviour	4	Behavio*			
Preconception	5	Preconception*.mp	Challenge	5	Challeng*.mp	Implementation	4	Implement*.mp
Expanded	6	Expanded.mp	Clinical utility	6	Clinical utility.mp			
Prenatal	7	Prenatal.mp	Decisional conflict	7	Decisional conflict.mp	Interview	5	Interview*.mp Interview/ Interviews as topic/
Reproductive	8	Reproduct*.mp						
			Decision-making	8	Decision?making.mp Decision Making/	Mixed method	6	Mixed method*.mp
			Experience	9	Experience*.mp	Pilot study	7	Pilot*.mp Pilot Projects/
			Informed consent	10	Informed consent.mp Informed Consent/	Program development or evaluation	8	Program*.mp Program development/ Program evaluation/
			Knowledge	11	Knowledge.mp Health Knowledge, Attitudes, Practice/	Randomised control trial	9	Randomi?sed control* trial*.mp Randomized Controlled Trials as Topic/
			Outcomes	12	Outcome*.mp	Survey/Questionnaire	10	Survey*.mp "Surveys and Questionnaires"/ Health surveys/ Health care surveys/
			Psychosocial	13	Psycho*.mp			
			Patient Satisfaction	14	Patient satisfaction.mp Patient satisfaction/			
			Reproductive behaviour	15	Reproduct* behavio*.mp Reproductive behaviour/	Qualitative	11	Qualitative*.mp Qualitative research/
			Understanding	16	Understand*.mp	Quantitative	12	Quantitative*.mp
			Uptake	17	Uptake.mp			
			Willingness to pay	18	Willingness to pay.mp			
RGCS Search		**(1 or 2 or 3 or 4) AND (5 or 6 or 7 or 8) (2213 articles)**	**Outcomes Search**		**1-18 (OR) (7343415 articles)**	**Methods Search**		**1-12 (OR) (2996983 articles)**

"((Genetic Carrier Screening OR Genetic Carrier Testing OR Carrier Screening OR Carrier Testing) AND (Preconception* OR Expanded OR Prenatal OR Reproduct*)) **AND** ((Acceptab* OR Barrier OR Behavio* OR Challeng* OR Clinical Utility OR Decisional Conflict OR Decision?Making OR Experience* OR Informed Consent OR Knowledge OR Outcome* or Psycho* OR Patient Satisfaction OR Reproduct* Behavio* OR Understand* OR Uptake OR Willingness to Pay) **OR** (Consensus* OR Feasib* OR Focus Group* OR Implement* OR Interview* OR Mixed Method* OR Pilot* OR Program* OR Randomi?ed control* trial* OR Survey* OR Qualitative* OR Quantitative*))"

Supplementary material B.2: COMET/CODECS taxonomy version 1.1

Outcome domains with definitions. Updates from previous iterations highlighted in blue

Core Area	Outcome Domain (COMET taxonomy)	Sub-domain (defined by SMG)	Definition	Example outcome
Physiological / clinical	Congenital, familial, and genetic outcomes	Primary outcomes of RGCS	Outcomes related to the results of RGCS	- *Carrier detection rate* - *Identification of increased risk couples*
		Secondary or incidental outcomes of RGCS	Outcomes related to laboratory findings not related to the primary indication for screening. This may include findings related to variants of uncertain significance, incidental findings (defined here are as findings that were unexpected), and secondary findings (defined here are secondary outcomes that were deliberately looked for and therefore are not truly incidental)	- *Identification of variants of uncertain significance* - *Identification of homozygous, hemizygous or compound heterozygous individuals at risk for developing one of the screened conditions*
		Other laboratory outcomes	Outcomes related to additional laboratory outcomes other than the primary results	- *Rate of test failure due to insufficient DNA in patient sample* - *Rate of false-positive screening via biochemical analysis*
	Pregnancy, puerperium, and perinatal outcomes	Pregnancy outcomes	Outcomes related to the impact of screening results on pregnancy outcomes.	- *Results of prenatal diagnosis* - *Decision to continue or terminate affected foetuses in future pregnancies* - *Number of individuals born with the condition(s) being screened for*
Life Impact	Cognitive functioning	Patient attitudes, perceptions and beliefs related to RGCS	Outcomes related to patient's attitudes, perceptions or beliefs about RGCS	- *Perception that RGCS would alter reproductive decisions* - *Attitude regarding recommending carrier screening to others*
		Deliberation and informed choice	Outcomes related to making an informed choice to undertake RGCS	- *Deliberation on the decision to accept or decline testing* - *Informed choice (congruence of attitudes, knowledge and test uptake)*

		Knowledge and understanding	Outcomes related to knowledge, incorporating concepts of understanding, recall and retention.	*- Understanding of the information received during genetic counselling session* *- Knowledge before and after pre-test genetic counselling*
	Delivery of care	Intention and uptake	Outcomes related to actual or intention to uptake an offer of RGCS	*- Uptake of RGCS* *- Intention to accept the offer of RGCS*
		Barriers, facilitators and factors influencing patient experience	Outcomes related to reasons for and against uptake of services, including offers of RGCS and further testing, as well as factors that influence experience of these services	*- Reasons for accepting/declining an offer of RGCS* *- Reasons or factors related to emotional reactions and psychological wellbeing* *- Sources of additional information used for decision-making regarding uptake of RGCS*
		Genetic counselling resource use	Outcomes related to the use and conduct of genetic counselling services	*- Number of post-test genetic counselling consultations* *- Time required for pre-test genetic counselling session*
		Goals of pre- and post-test genetic counselling	Outcomes related to the patient experience of pre- and post-test interactions with their health providers	*- Genetic counselling supported informed decision-making* *- Timing and method of information provision promoted understanding*
		Practice guidelines/recommendations	Outcomes related to clinical practice recommendations	*- Ordering clinicians selection of conditions according to practice recommendations*
		Patient preferences	Outcomes related to patient preferences regarding the offer of RGCS	*- Preference regarding individual or couple-based results* *- Preference regarding conditions included in RGCS*
		Patient satisfaction with the processes of RGCS	Outcomes related to patient satisfaction with services related to RGCS	*- Satisfaction with pre-test genetic counselling*
		Timeliness	Outcomes related to the timeliness of delivery of care in RGCS programs	*- Mean gestational age at time of reproductive carrier screening* *- Offer of reproductive carrier screening to women before 10 weeks gestation*
	Emotional functioning/ wellbeing	Decision satisfaction and regret	Outcomes related to decisional satisfaction or regret at a later timepoint	*- Distress or remorse after a healthcare decision measured at a later timepoint* *- Satisfaction with the decision to accept/decline screening*

		Psychological wellbeing	Outcomes related to the psychological impact of RGCS	- *Anxiety (measured at a range of timepoints)* - *Subjective distress associated with being identified as a heterozygote, at a later timepoint*
	Perceived health status	Perception of personal health status after RGCS	Outcomes related to the impact of RGCS on perception of personal health	- *Impact of results on perception of own health*
	Personal circumstances	Decision-making (non-reproductive)	Outcomes related to the impact of results on decisions other than reproductive planning	- *Impact of negative result on decisions related to insurance, healthcare and lifestyle* - *Number of prospective marriages cancelled due to identification as an increased risk couple (pre-marital screening programs)*
		Decision-making (reproductive)	Outcomes related to impact of results on decision-making for reproductive planning, including perceived or actual impact on these decisions	- *Pursued or planned to pursue alternate reproductive options* - *Intended reproductive decisions if identified as an increased risk couple*
		Familial implications	Outcomes related to the impact of results of patient relationships	- *Impact of results on couple's relationship* - *Number of heterozygotes that informed family members of their results*
		Perceived utility of RGCS	Outcomes related to patient's perceptions of the impact of RGCS and how they utilised the results	- *Confidence or empowerment related to reproductive decision-making* - *Results were available in a timely manner that allowed for consideration and decision-making*
	Social functioning	Acceptability of further testing or alternative reproductive options	Outcomes related to patients' perspectives on prenatal diagnosis, termination of pregnancy, and preimplantation genetic diagnosis	- *Religious views on PND, PGD and TOP* - *Patient perceptions of practical difficulties of IVF and PGD*
		Privacy concerns and stigmatisation	Outcomes related to the impact of results on privacy and stigmatisation	- *Concern regarding privacy or confidentiality* - *Fear of discrimination by insurance companies*
Resource Use	Need for further intervention	Further testing	Outcomes related to the use of further testing for various purposes including clarifying reproductive risk as a couple, testing during a pregnancy, or electing PGD	- *Uptake of partner testing* *-Uptake of prenatal diagnosis in increased risk pregnancies at the time of screening* - *Uptake of postnatal diagnostic testing in decliners of prenatal diagnosis in a current pregnancy at the time of screening* - *Uptake of preimplantation genetic diagnosis in increased risk couples*

The development of the CODECS outcome domains was an iterative process, initially compiled at the completion of the quantitative systematic review (Version 1.0 – Appendix A). It was then reviewed and updated at the completion of the qualitative systematic review (Version 1.1 – Appendix B), with the addition of 3 new outcome domains and revisions to the wording of a number of domains and definitions to further clarify and expand on the initial domains. Finally, these were reviewed and revised at the completion of the qualitative interview study (Version 1.2 – Appendix C).

Version 1.1 – defined at completion of the qualitative systematic review, in which 3 new domains were identified. Documented updates to CODECS domains (indicated in blue) and summarised below. Following revisions 25 outcome domains remain:

Wording changes: "Genetic counselling" was changed to "Genetic counselling resource use", "Knowledge" was changed to "Knowledge and understanding", "Barrier and facilitators" was changed to "Barriers, facilitators, and factors influencing patient experience", "Attitudes and perceptions" was changed to "Patient attitudes, perceptions and beliefs related to RGCS", "Patient satisfaction" was changed to "Patient satisfaction with the processes of RGCS"; "Intention and uptake" was changed to "Uptake of services"
Domain changes: "Information sources" was merged with "Barriers, facilitators, and factors influencing patient experience"; "postnatal outcomes" was merged with "pregnancy outcomes"

Supplementary material B.3: Summary of included studies

Study ID	Author and Year	Publication Title	Country	Test Type	Study Design	Sequential Review Status	Number of Outcomes
1	Ioannou et al. 2015[1]	"Suddenly having two positive people who are carriers is a whole new thing" - experiences of couples both identified as carriers of cystic fibrosis through a population-based carrier screening program in Australia	Australia	CF only	Mixed Methods Associated publications from quantitative review[2,3]	Qualitative review only	32
2	Cousens et al. 2013[4]	"He didn't say that thalassaemia might come up" - beta-thalassaemia carriers' experiences and attitudes	Australia	Haemoglobinopathies	Qualitative only	Qualitative review only	17
3	Beard et al. 2016[5]	"I'm healthy, it's not going to be me": exploring experiences of carriers identified through a population reproductive genetic carrier screening panel in Australia	Australia	3-gene	Qualitative only	Qualitative review only	24
4	Tardif et al. 2018[6]	Experience of carrier couples identified through a population-based carrier screening pilot program for four founder autosomal recessive diseases in Saguenay-lac-Saint-Jean	Canada	Founder	Qualitative only	Qualitative review only	14
5	Frumkin et al. 2011[7]	"The most important test you'll ever take": attitudes toward confidential carrier matching and open individual testing among modern-religious jews in Israel	Israel	Founder	Qualitative only	Qualitative review only	14

6	Holtkamp et al. 2019[8]	Direct-to-consumer carrier screening for cystic fibrosis via a hospital website: a 6-year evaluation	The Netherlands	CF only	Qualitative only	Qualitative review only	8
7	Mathijssen et al. 2018[9]	Preconception carrier screening for multiple disorders: evaluation of a screening offer in a Dutch founder population	The Netherlands	Founder	Mixed Methods Associated publications from quantitative review[10]	Included in both reviews	9
8	Holtkamp et al. 2018[11]	Experiences of a high-risk population with prenatal hemoglobinopathy carrier screening in a primary care setting: a qualitative study	The Netherlands	Haemoglobinopathies	Qualitative only	Qualitative review only	15
9	Dormandy et al. 2010[12]	Antenatal screening for haemoglobinopathies in primary care: a cohort study and cluster randomised trial to inform a simulation model. The screening for haemoglobinopathies in first trimester (shift) trial	UK	Haemoglobinopathies	Mixed Methods Publications from quantitative review[13,14]	Included in both reviews	17
	Tsianakas et al. 2012[15]	Offering antenatal sickle cell and thalassaemia screening to pregnant women in primary care: a qualitative study of women's experiences and expectations of participation	UK	Haemoglobinopathies	Mixed Methods Publications from quantitative review[13,14]	Qualitative review only	

10	Lewis et al. 2012[16]	Reproductive empowerment: the main motivator and outcome of carrier testing	UK	Unspecified	Qualitative only	Qualitative review only	11
	Clarke et al. 2018[17]	Assessment of willingness to pay for expanded carrier screening among women and couples undergoing preconception carrier screening	USA	ECS	Mixed Methods Publications from quantitative review[18,19]	Included in both reviews	
11	Kraft et al. 2018[20]	Patient actions and reactions after receiving negative results from expanded carrier screening	USA	ECS	Mixed Methods Publications from quantitative review[18,19]	Included in both reviews	18
	Kraft et al. 2018[21]	Patient perspectives on the use of categories of conditions for decision making about genomic carrier screening results	USA	ECS	Mixed Methods Publications from quantitative review[18,19]	Qualitative review only	
12	Rothwell et al. 2017[22]	Experiences among Women with Positive Prenatal Expanded Carrier Screening Results	USA	ECS	Qualitative only	Qualitative review only	17
13	Kalfoglou et al. 2011[23]	Orthodox Ashkenazi Young Adults' Knowledge, Experiences, Attitudes, and Beliefs About Genetic Carrier Testing	USA	Founder	Qualitative only	Qualitative review only	11

Supplementary material B.4: Risk of bias assessment.

Higher scores represent higher quality and less risk of bias on a scale of 0-1

First Author and Year	QualSyst Score
Beard (2016)[5]	0.75
Clarke (2018)[17]	0.6
Cousens (2013)[4]	0.8
Dormandy (2010)[12]	0.6
Frumkin (2011)[7]	0.45
Holtkamp (2018)[11]	0.8
Holtkamp (2019)[8]	0.7
Ioannou (2015)[1]	0.75
Kalfoglou (2011)[23]	0.6
Kraft (2018)_1)[20]	0.5
Kraft (2018)_2)[21]	0.55
Lewis (2012)[16]	0.85
Mathijssen (2018)[9]	0.6
Rothwell (2017)[22]	0.7
Tardif (2018)[6]	0.75
Tsianakas (2012)[15]	0.7

Supplementary material B.5: List of outcomes extracted from qualitative studies

COMET Core Area	COMET Domains	CODECS Domains	ID	Outcome Description
Physiological and clinical outcomes	Congenital, familial, and genetic outcomes	Primary outcomes of RGCS	1	Carrier detection rate/carrier status of participants
	Pregnancy, puerperium, and perinatal outcomes	Pregnancy outcomes	2	Results of prenatal diagnosis
			3	Decision to continue or terminate a pregnancy identified as affected through prenatal diagnosis
Life impact	Cognitive functioning	Attitudes and perceptions	4	Perceived risk of being a carrier
			5	Belief that offering RGCS facilitates informed decisions
			6	Perception of the importance of RGCS
			7	Positive views of the RGCS offer
			8	Willingness to pay as a proxy for personal utility
		Deliberation and informed choice	9	Deliberation
			10	Engagement in decision-making
			11	Voluntariness - Patient's recalled being given the choice to accept or decline RGCS
			12	Information needs were met and supported informed decision-making
		Knowledge and understanding	13	Awareness of the condition(s) tested prior to the screening offer
			14	Correct understanding of the purpose of testing and implications of results

COMET Core Area	COMET Domains	CODECS Domains	ID	Outcome Description
Life impact	**Emotional functioning and wellbeing**	**Psychological wellbeing**	15	Anxiety
			16	Distress
			17	Stress
			18	Worry
			19	Conceiving became less spontaneous
			20	Curiosity
			21	Detachment from current pregnancy
			22	Difficulty being happy to fall pregnant
			23	Grief
			24	Relief
			25	Shock
			26	Surprise
		Decision satisfaction and regret	27	Retrospective satisfaction with the decision to have RGCS (T2: Post-test, T4: long-term)
			28	Regret related to a healthcare decision at a later timepoint
	Social functioning	**Privacy concerns and stigmatisation**	29	Concerns regarding stigmatisation
			30	Concerns regarding privacy or confidentiality
			31	Concerns regarding insurance
		Acceptability of further testing or alternative reproduction options	32	Personal preferences regarding PND, PGD and TOP
			33	Religious views on PND, PGD and TOP

COMET Core Area	COMET Domains	CODECS Domains	ID	Outcome Description
Life impact	Delivery of care	Barriers and facilitators	34	Reasons or factors influencing uptake of RGCS
			35	Reasons or factors influencing uptake of further testing and prenatal decisions
			36	Barriers to patient understanding of RGCS
			37	Reasons or factors related to emotional reactions and psychological wellbeing
		Goals of pre- and post-test genetic counselling	38	Genetic counselling supported informed decision-making (T1: pre-test, T2: post-test)
			39	Genetic counselling provided sufficient information to meet patient needs (T1: pre-test, T2: post-test)
			40	Genetic counselling presented screening and further testing as a choice (T1: pre-test, T2: post-test)
			41	Genetic counselling promoted reproductive empowerment (T2: post-test)
			42	Genetic counselling was accessible (T2: post-test)
			43	Genetic counselling provider was knowledgeable and empathetic (T2: post-test)
			44	Timing and method of information provision promoted understanding (T1: pre-test)
			45	Patient's perceived pre-test counselling as necessary (T1: pre-test)
		Patient preferences	46	Preference regarding conditions included in RGCS
			47	Preference regarding health professionals offering RGCS
			48	Preference regarding sharing results with other healthcare providers
			49	Preference regarding the timing and setting of RGCS
			50	Preference regarding the format of results e.g. individual, couple, Dor Yesharim
		Patient satisfaction	51	Satisfied with the convenience of screening processes
			52	Concerns regarding cost and accessibility

COMET Core Area	COMET Domains	CODECS Domains	ID	Outcome Description
Life impact	**Delivery of care**	**Timeliness**	53	RGCS should be offered as early as possible in the prenatal setting/Gestational age when offered screening
			54	Further testing was arranged in a timely manner (T2: post-test)
			55	RGCS should ideally be offered preconception
	Personal circumstances	**Decision-making (non-reproductive)**	56	Decisions regarding long-term care, disability or life insurance
			57	Decision to proceed with a marriage due to identification as an increased risk couple (e.g. Dor Yesharim)
			58	Lifestyle changes
		Decision-making (reproductive)	59	Results influenced decision to continue or terminate an affected pregnancy
			60	Results influenced decisions about having children or family size
			61	Uptake of PGD in subsequent pregnancies/ Pursued or planned to pursue alternate reproductive options
			62	Results influenced decisions about other prenatal testing options
			63	Patient's sought sources of additional information to assist with reproductive decisions e.g., support groups
			64	Uptake of partner testing
			65	Uptake of prenatal diagnosis
		Familial implications	66	Patients informed at-risk family members
			67	Patients informed actual or potential reproductive partners
			68	Patient support needs for dissemination
			69	Reasons or factors influencing decision to disseminate information regarding carrier status

COMET Core Area	COMET Domains	CODECS Domains	ID	Outcome Description
		Perceived utility of RGCS	70	Results were available in a timely manner that allowed for consideration and decision-making
			71	Patients reported a sense of confidence and empowerment related to reproductive decisions
Resource use	**Need for intervention**	**Further testing**	72	Mention/uptake of partner testing
			73	Mention/uptake of prenatal diagnosis

Supplementary material B.6: Block diagram of outcomes reported per study
(n=13; consisting of 16 publications). Outcome IDs from Table 4, studies listed in footnotes

COMET Core Area	COMET Domains	CODECS Domains	Outcome ID	Study 1	Study 2	Study 3	Study 4	Study 5	Study 6	Study 7	Study 8	Study 9	Study 10	Study 11	Study 12	Study 13
Physiological and clinical outcomes	Congenital, familial, and genetic outcomes	Primary laboratory outcomes	1	■	■		■	■	■		■	■		■	■	■
	Pregnancy, puerperium, and perinatal outcomes	Pregnancy outcomes	2						■							
			3						■						■	
Life impact	Cognitive functioning	Attitudes and perceptions	4						■			■	■		■	■
			5										■	■		
			6	■					■			■	■			■
			7	■									■			
			8		■											
		Deliberation and informed choice	9								■		■			
			10							■						
			11	■			■		■			■				
			12	■			■					■			■	

COMET Core Area	COMET Domains	CODECS Domains	Outcome ID	Study 1	Study 2	Study 3	Study 4	Study 5	Study 6	Study 7	Study 8	Study 9	Study 10	Study 11	Study 12	Study 13
Life impact	Cognitive functioning	Knowledge and understanding	13						■				■			■
			14				■	■							■	
	Emotional functioning and wellbeing	Psychological wellbeing	15		■				■			■			■	
			16				■		■							
			17		■					■		■				
			18		■	■			■							
			19			■										
			20		■											
			21									■				
			22													■
			23			■		■	■			■				■
			24		■				■		■				■	
			25			■	■	■	■			■				■
			26						■						■	■

COMET Core Area	COMET Domains	CODECS Domains	ID	Study 1	Study 2	Study 3	Study 4	Study 5	Study 6	Study 7	Study 8	Study 9	Study 10	Study 11	Study 12	Study 13
Life impact	Emotional functioning and wellbeing	Decision satisfaction and regret	27		■	■										■
			28						■							
	Social functioning	Privacy concerns and stigmatisation	29			■		■		■						
			30		■											
			31		■											
		Acceptability of further testing or alternative reproduction options	32					■		■			■			
			33					■		■			■			
	Delivery of care	Barriers and facilitators	34	■	■		■	■	■	■	■	■	■	■	■	■
			35				■		■		■		■			
			36	■												
			37			■	■		■			■			■	■
		Goals of pre- and post-test genetic counselling	38	■			■		■	■					■	
			39	■	■		■		■	■		■			■	
			40	■			■		■							

COMET Core Area	COMET Domains	CODECS Domains	ID	Study 1	Study 2	Study 3	Study 4	Study 5	Study 6	Study 7	Study 8	Study 9	Study 10	Study 11	Study 12	Study 13
Life impact	Delivery of care	Goals of pre- and post-test genetic counselling	41								■					
			42				■					■				
			43								■	■			■	
			44	■	■				■				■	■		
			45				■									
		Patient preferences	46		■					■		■		■	■	■
			47	■									■			
			48		■											
			49	■			■	■				■	■	■		
			50					■		■						
		Patient satisfaction	51						■			■	■	■		
			52						■			■				
		Timeliness	53	■												
			54									■				
			55	■			■						■	■		
	Personal circumstances	Decision-making (non-reproductive)	56		■											
			57					■		■						
			58		■											

COMET Core Area	COMET Domains	CODECS Domains	ID	Study 1	Study 2	Study 3	Study 4	Study 5	Study 6	Study 7	Study 8	Study 9	Study 10	Study 11	Study 12	Study 13
Life impact	Personal circumstances	Decision-making (reproductive)	59					■	■						■	
			60			■										■
			61						■							
			62		■											
			63						■		■					
			64												■	
			65						■		■					
		Familial implications	66						■		■	■				
			67					■								
			68						■							
			69						■			■				
		Perceived utility of RGCS	70	■												
			71		■	■					■				■	■
Resource use	Need for intervention	Further testing	72	■			■					■				
			73						■			■				

Study 1 – *Dormandy (2010)*[12]*; Tsianakas (2012)*[15]*;* **Study 2** – *Clarke (2018)*[17]*, Kraft (2018)*[20]*, Kraft (2018)*[21]*;* **Study 3** – *Mathijssen (2018)*[9]*;* **Study 4** – *Cousens (2013)*[4]*;* **Study 5** – *Frumkin (2011)*[7]*;* **Study 6** – *Ioannou (2015)*[1]*;* **Study 7** – *Kalfolgou (2011)*[23]*;* **Study 8** – *Lewis (2012)*[16]*;* **Study 9** – *Beard (2016)*[5]*;* **Study 10** – *Holtkamp (2018)*[11]*;* **Study 11** – *Holtkamp (2019)*[8]*;* **Study 12** – *Rothwell (2017)*[22]*;* **Study 13** – *Tardif (2018)*[6]

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Appendix C – Supporting information for Chapter 5

Summary of Content

Supplementary material C.1: Guidance informed study design

Summary of available guidance for conducting a qualitative study during COS development and resulting methodological choices

COMET INITIATIVE GUIDANCE	OUR STUDY DESIGN
Begin with a broad narrative approach before narrowing in to research or COS-specific questions	Our interview schedule is designed with this broad-to-narrow approach in mind (see figure X)
An example of research outcomes should be provided, with care not to bias participants	We provided an example that was not specific to RGCS but was a relatable example encompassing potential research outcomes of COVID-19
Patient research partners should be involved in the development of the interview schedule	Two patient research partners were consulted regarding the best approach to eliciting outcomes in this study. The idea of the word association exercise resulted from a co-design/brainstorming session with one patient research partner, and was then discussed and piloted with the other for approval.
Guidance provided is not prescriptive, approaches to using qualitative methods for COS development should be transparently reported to allow others working in the area to learn from different methods	We collected feedback from participants regarding the novel word association exercise approach to eliciting outcomes as preliminary data to inform the use of this method in future studies. We plan to clearly and transparently report the content of our interview schedule for the wider COS community to learn from.

Supplementary material C.2 – Social media expressions of interest

Online Parenting Website Forums

Did you have genetic testing when planning to start your family or during your pregnancy? If so, the University of Technology Sydney would like to invite you to participate in research about your experience.

We are interested in hearing the views of individuals or couples who have had a type of genetic testing called **reproductive genetic carrier screening**. Other names for this test include preconception carrier screening or expanded carrier screening. We want to involve participants who have a range of experiences of this testing and encourage anyone who thinks they may be eligible to register their interest.

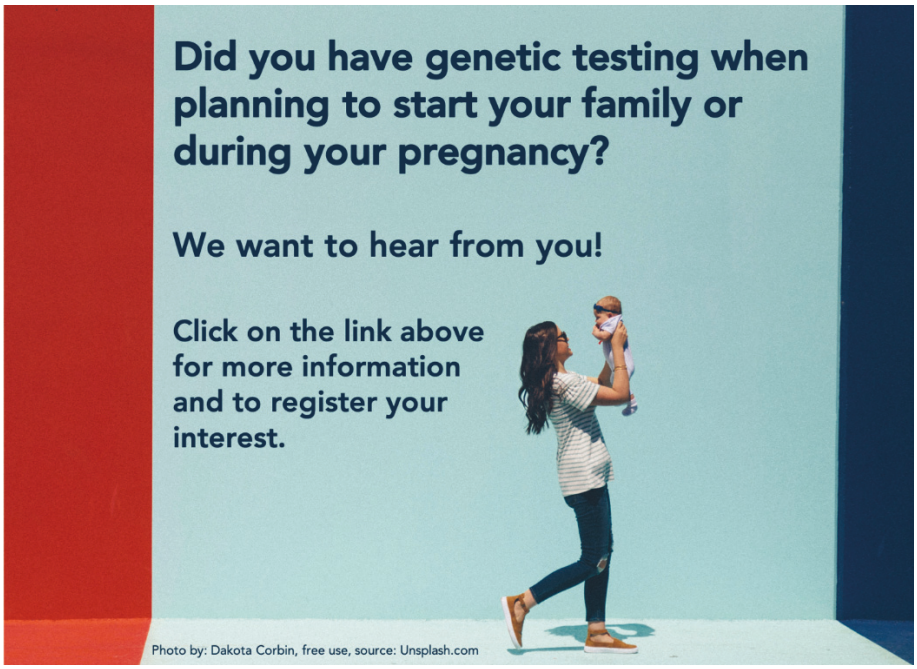
You will be invited to join a one-on-one interview with a researcher and can participate on your own or with your partner. We will run the interviews virtually using a software called Zoom, meaning you can participate from the comfort of your own home.

For more information and to register your interest, please visit: https://tinyurl.com/r9cnf4xt

Thank you!

Twitter

Did you have genetic testing when planning to start your family or during your pregnancy? If so, researchers @UTS_GeneticCounselling would like to invite you to participate in research about your experience. We are interested in hearing from individuals or couples who have had a type of genetic testing called **reproductive genetic carrier screening**. Follow the link for more information and to register your interest https://tinyurl.com/r9cnf4xt



"Genetic Carriers – Pregnancies" Facebook Group

Are you interested in talking about your experience of reproductive genetic carrier screening and being identified as a carrier? If so, the University of Technology Sydney would like to invite you to participate in research about your experience.

You may join an online focus group with up to 6 others who have had reproductive carrier screening, or have an online one-on-one interview with a researcher if you prefer. We appreciate that family planning and pregnancy can be a sensitive topic to discuss, so we will ask you choose either a focus group or a one-on-one interview when you register your interest. You can participate on your own or with your partner. We will run the focus groups and the interviews virtually using a software called Zoom, meaning you can participate from the comfort of your own home.

For more information and to register your interest, please visit:
https://tinyurl.com/r9cnf4xt

Thank you!

Kind regards,
Ebony Richardson
Associate Genetic Counsellor | PhD Candidate
University of Technology Sydney
ebony.j.richardson@student.uts.edu.au

Supplementary material C.3: Eligibility and demographic survey

Thank you for expressing interest in participating in our research project!

What is this study about?
Researchers at the University of Technology Sydney are conducting a research study about patient experiences of reproductive genetic carrier screening. In healthcare, when a new type of test becomes available we need evidence about its benefits and harms to make decisions about whether to offer this test to our patients. Evidence is gathered by researchers who look at the effect of the new test on the patient by measuring 'outcomes'. An outcome is any measurable effect of the test. For example, an outcome of a genetic test might include:

- Detection of a genetic variant, or mutation, that is known to cause disease or increase risk of disease
- Psychological harms, such as increased anxiety caused by the testing process or test result
- Behaviour change, such as deciding to have invasive testing during a pregnancy

By talking to us about your experience, you can help us to find out what outcomes are important to patients that access reproductive genetic carrier screening.

We are recruiting people who have had reproductive genetic carrier screening to participate in this study. Individuals with low risk or high risk results are eligible to participate, in fact we want to talk to as many people as possible so that we can understand a range of experiences.

What else do I need to know?
If you decide to participate, we will invite you to participate in either a focus group with other people who have had reproductive genetic carrier screening, or a one-on-one interview with our primary researcher. You can decide which of these options you would prefer. Both options will be held virtually, using an online platform called Zoom. This is aimed at making participation as accessible as possible, and maximising your comfort by being able to participate from your own home.

Focus groups: Focus groups will be approximately 2 hours in duration and will be held at flexible times, with the option of early evening or on a weekend to allow them to fit within your schedule. A quick online survey will be used to determine a time that suits everyone. There will be 6-8 participants in your focus group and you will be matched with those that have had a similar experience of reproductive carrier screening to you.

One-on-one interviews: Interviews will be up to 1 hour, but may take less time, and can be held during flexible hours to fit within your schedule. You will meet with our primary researcher, and may also have a second researcher present to take additional notes.

Both focus groups and one-on-one interviews will be video and audio recorded using the online platform, Zoom.

To be eligible for this study, you must be aged 18 or over and have sufficient English to participate in a focus group or interview with a researcher. Your participation is completely voluntary, and any information you provide to the research team will be confidential.

For more information please read the **Participant Information Sheet**

This study has received Ethics approval from The University of Technology Sydney Ethics Committee (UTS HREC ETH20-5179)

If you are interested in participating in this study, please complete the eligibility survey. Your survey data will be collected and retained by University of Technology Sydney researchers. We will not use this data for any purpose except to determine your eligibility for the study. If you are eligible to participate, a member of the research team will contact you to discuss the study further.

By clicking on the 'Next' button below, you are indicating that you understand that the data that you provide in this survey will be collected and retained by researchers from the University of Sydney. If you do not wish to continue to the eligibility survey, please close your browser window to exit the survey.

What is your name?

_____

Are you aged 18 years or older?

_____

Which city and country do you currently live in?

_____

Are you currently pregnant?

❍ **Yes**
❍ **No**

Have you had reproductive genetic carrier screening as part of your pregnancy healthcare or in planning for future pregnancies?

Reproductive genetic carrier screening is a test that is available through GPs, obstetrician/gynaecologists, midwives, genetic counsellors, or clinical geneticists. A blood or saliva sample is collected and tested for genetic variants or mutations that indicate if you are a carrier for a genetic condition. For most genetic conditions included in this type of test, both reproductive partners need to be carriers for there to be a risk of their child inheriting this condition. These are called recessive conditions. The test may also look for conditions that can be inherited if only the mother is a carrier, these are called X-linked conditions. Common examples of conditions that are tested in reproductive genetic carrier screening are cystic fibrosis, spinal muscular atrophy, fragile X, and Tay Sachs disease. Some available tests may look for hundreds or thousands of conditions.

You may know this test by other names such as preconception carrier screening or ethnicity-based carrier screening. You may also recognise this test by a commercial name, such as Horizon Carrier Screening, Beacon Expanded Carrier Screening, Myriad Counsyl Foresight Carrier Screening, or Eugene Carrier Screening.

If you are unsure if you have had the right type of testing to be eligible for this research, select unsure and we will contact you to ask some extra questions.

❍ **Yes, I have had reproductive genetic carrier screening during pregnancy**
❍ **Yes, I have had reproductive genetic carrier screening before pregnancy (preconception)**
❍ **Unsure**

What prompted you to have reproductive genetic carrier screening?

❍ **I had a family history of a genetic condition that I was concerned about**
❍ **I am from an ethnic background that has an increased risk of certain genetic conditions**
❍ **I just wanted to be pro-active**
❍ **Other _____**

What was the result of your test?

❍ **I was tested first and was not found to be a carrier, so we didn't test my partner**
❍ **My partner and I were tested at the same time and neither of us were found to be carriers of a genetic condition**
❍ **I was found to be a carrier for one or more genetic conditions, but my partner was not a carrier for the same conditions**
❍ **My partner and I were both tested and were found to be carriers of the same genetic condition**
❍ **I was found to be a carrier of an X-linked condition**
❍ **Other _____**

Would you prefer to participate in:

❍ **Focus group**
❍ **One-on-one interview**
❍ **Either**

Please provide your email address so that we can contact you:

_____

Supplementary material C.4: Emails to respondents/participants

---

Initial Email to Respondents

Subject line: Research Study - Reproductive Genetic Carrier Screening

[For Australia, interview]

Dear [name],

Thank you for indicating your interest in our research study and for providing your contact details. I am looking forward to speaking with you.

I want to ensure that we select a time that is most appropriate for you, so if you let me know your preference regarding time (morning, afternoon or evening) and day of the week we can get a time set up. It is important that you are in a private place, such as at home or in a private office at work, with minimal distractions during the interview, so please take this into account when suggesting a time.

We also have the option for couples to participate together, so please let me know if your partner would like to join. Thank you once again for your interest, feel free to get in touch if you have any questions.

Kind regards,

[For international] - check time zone and propose most suitable times

Dear [name],

Thank you for indicating your interest in our research study and for providing your contact details. I am looking forward to speaking with you.

I want to ensure that we select a time that is most appropriate for you whilst catering to different time zones. I am based in Sydney, Australia, so it would be ideal for us to meet between [3pm-7pm, [City] time] (which corresponds to 6am-9am my time). If you let me know your preference regarding time and day of the week, we can find a suitable time. It is important that you are in a private place, such as at home or in a private office at work, with minimal distractions during the interview, so please take this into account when suggesting a time.

We also have the option for couples to participate together, so please let me know if your partner would like to join. Thank you once again for your interest, feel free to get in touch if you have any questions.

Kind regards,

Follow-up for Unsure Respondents

Hi [name],

Thank you for indicating your interest in our research study and for providing your contact details. I can see that you have indicated that you are unsure if you have had the right type of testing to be eligible for this study.

To help me determine whether you have had reproductive carrier screening could you provide me with a bit of background information about any genetic testing you can remember having? In particular any genetic testing that you had during a pregnancy or in preparation for getting pregnant.

Some helpful prompts are:

- Who did you have genetic testing through – was it a GP, an obstetrician, a genetic counsellor?
- Do you remember any conditions that were specifically looked at? Common examples in Australia are cystic fibrosis, spinal muscular atrophy and Fragile X syndrome.
- This testing is different to screening for chromosome conditions like Down syndrome that most women have during pregnancy. This is an extra test that some women choose to have, which can be done before or during pregnancy and usually has an out-of-pocket cost of between $250-$750.
- Carrier screening usually involves testing the female partner first, and if they are found to be a carrier, their male partner is also tested.

Thank you again for expressing your interest in participating. Any information you provide will be kept strictly confidential and will only be used to determine your eligibility to participate in this study.

Kind regards,

Prompt for Unsure Respondents

Hi [name],

I am following up on my email below regarding a research study that you expressed interest in. This is a reminder to consider the below questions to determine if you have had reproductive genetic carrier screening and would be eligible to participate in my research.

If I do not hear from you, I will assume that you are not eligible and would prefer not to be contacted further.

Kind regards,

Zoom link email
Hi [name],

Thank you for finding a suitable time to participate in this research study. We have agreed to meet on [Friday 4th June at 1pm], for approximately 1 hour.

Please use this link to join: [insert link]

Full meeting details are available below if needed. Please have a pen and paper handy as I will be asking you to write some things down during the interview.

I look forward to speaking with you.

Kind regards,

No-response reminder after initial email

Hi [name],

I wanted to follow up on my previous email to see if you are still interested in participating in my research study. If you are, let me know your preferences regarding dates and times and we can book in an interview.

Kind regards,

Supplementary material C.5: Participant information sheet

UTS HREC Reference No: ETH20-5179

The CODECS Study: Core Outcome Development for Carrier Screening

WHO IS DOING THE RESEARCH?

My name is Ebony Richardson and I am a student at UTS. My supervisor is Dr Chris Jacobs, who can be contacted at chris.jacobs@uts.edu.au

WHAT IS THIS RESEARCH ABOUT?

This research is to find out about outcomes that are important for people that have reproductive genetic carrier screening. In healthcare, when a new type of test becomes available we need evidence about its benefits and harms to make decisions about whether to offer this test to our patients. Evidence is gathered by researchers who look at the effect of the new test on the patient by measuring 'outcomes'. An outcome is any measurable effect of the test. For example, an outcome of a genetic test might include:

- Detection of a genetic variant, or mutation, that is known to cause disease or increase risk of disease
- Psychological impact, such as increased anxiety caused by the testing process or test result
- Behaviour change, such as deciding to have invasive testing during a pregnancy

Reproductive genetic carrier screening is a blood or saliva test that is available through your GP, obstetrician/gynaecologist, genetic counsellor, or clinical geneticist. It assesses whether you are a carrier for a genetic condition, and whether your reproductive partner is also a carrier. For most genetic conditions included in this type of test, both reproductive partners need to be carriers for there to be a risk of passing the condition on to their child. These are called recessive conditions. It may also look for conditions that can be passed on if only the mother is a carrier, these are called X-linked conditions. Common examples of conditions that are tested in reproductive genetic carrier screening are cystic fibrosis, spinal muscular atrophy, fragile X, and Tay Sachs disease. Some available tests may look for hundreds or thousands of conditions.

You may know this test by other names such as preconception carrier screening or expanded carrier screening. You may also recognise this test by a commercial name, such as Horizon Carrier Screening, Beacon Expanded Carrier Screening, Myriad Counsyl Foresight Carrier Screening, or Eugene Carrier Screening.

If you have been invited to participate in this study, you have had reproductive genetic carrier screening as part of your pregnancy health care or in planning for future pregnancies. We want to understand your experience of reproductive genetic carrier screening and how it has impacted you. Using your experience, we will gain an understanding of what outcomes are important to patients that have this testing.

WHY HAVE I BEEN ASKED?

You have been invited to participate in this study because you have had reproductive genetic carrier screening as part of your pregnancy health care or in planning for future pregnancies.

IF I SAY YES, WHAT WILL IT INVOLVE?

If you decide to participate, we will invite you to participate in either a focus group with other people who have had reproductive genetic carrier screening, or a one-on-one interview with our primary researcher. You can decide which of these options you would prefer. Both options will be held virtually, using an online platform called Zoom. This is aimed at making participation as accessible as possible, and maximising your comfort by being able to participate from your own home.

Focus groups: will be approximately 2 hours in duration and will be held at flexible times, with the option of early evening or on a weekend to allow them to fit within your schedule. A quick online survey will be used to determine a time that suits everyone. There will be 6-8 participants in your focus group and you

will be matched with those that have had a similar experience of reproductive genetic carrier screening to you.
One-on-one interviews: will be up to 1 hour, but may take less time, and can be held during flexible hours to fit within your schedule. You will meet with our primary researcher, and may also have a second researcher present to take additional notes.

Both focus groups and one-on-one interviews will be video and audio recorded using the online platform, Zoom. After your focus group/interview you will be asked if you are interested in participating in the next phase of this research which will take place in a few month's time.

ARE THERE ANY RISKS/INCONVENIENCE?

Yes, there are some risks/inconvenience. You may be asked sensitive questions about your reproductive decisions, pregnancy experience, or family planning. You will always have the option to decline answering any questions that make you uncomfortable. As this can be a sensitive topic, you may experience some discomfort or distress in recalling your experience. We encourage you to let us know if this happens and we can take a break or end the session. Psychological support will be provided for any distress caused as a result of recounting your experience.

DO I HAVE TO SAY YES?

Participation in this study is voluntary. It is completely up to you whether or not you decide to take part.

WHAT WILL HAPPEN IF I SAY NO?

If you decide not to participate, it will not affect your relationship with the researchers or the University of Technology Sydney. If you wish to withdraw from the study once it has started, you can do so at any time without having to give a reason, by contacting Ebony Richardson on ebony.j.richardson@student.uts.edu.au

However, it may not be possible to withdraw your data from the study results if these have already had your identifying details removed.

If you decide to leave the research project, we will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

CONFIDENTIALITY

By giving your verbal consent, you consent to the research team collecting and using personal information about you for the research project. All this information will be treated confidentially. Your information will be stored securely and will only be accessible to the primary researcher, Ebony Richardson, and my supervisor, Dr Chris Jacobs.

We would like to store your information for future use in research projects that are an extension of this research project. In all instances your information will be treated confidentially.

We plan to publish the results of this study in medical journals. In any publication, information will be provided in such a way that you cannot be identified.

WHAT IF I HAVE CONCERNS OR A COMPLAINT?

If you have concerns about the research that you think I or my supervisor can help you with, please feel free to contact us on chris.jacobs@uts.edu.au or ebony.j.richardson@student.uts.edu.au

You will be given a copy of this form to keep.

NOTE:
This study has been approved in line with the University of Technology Sydney Human Research Ethics Committee [UTS HREC] guidelines. If you have any concerns or complaints about any aspect of the conduct of this research, please contact the Ethics Secretariat on ph.: +61 2 9514 2478 or email: Research.Ethics@uts.edu.au], and quote the UTS HREC reference number. Any matter raised will be treated confidentially, investigated and you will be informed of the outcome.

Supplementary material C.6: COMET/CODECS taxonomy version 1.2

Core Area	Outcome Domain (COMET taxonomy)	Sub-domain (defined by SMG)	Definition	Example outcome
Physiological / clinical	Congenital, familial, and genetic outcomes	Primary laboratory outcomes	Outcomes related to the core findings or results reported in RGCS	*- Carrier detection rate/carrier status of participants* *- Identification of increased risk couples*
		Secondary or incidental laboratory outcomes	Outcomes related to laboratory findings not related to the primary indication for screening.	*- Identification of variants of uncertain significance* *- Identification of homozygous, hemizygous or compound heterozygous individuals at risk for developing one of the screened conditions*
		Technical laboratory outcomes	Outcomes related to technical or practical considerations of RGCS from the laboratory perspective	*- Rate of test failure due to insufficient DNA in patient sample* *- Rate of laboratory error (false negatives or false positives)*
	Pregnancy, puerperium, and perinatal outcomes	Pregnancy outcomes	Outcomes related to the impact of screening results on pregnancy outcomes.	*- Results of prenatal diagnosis* *- Decision to continue or terminate affected foetuses in future pregnancies* *- Number of individuals born with the condition(s) being screened for*
Life Impact	Cognitive functioning	Patient attitudes, perceptions and beliefs related to RGCS	Outcomes related to patient's attitudes, perceptions or beliefs about RGCS	*- Perception that RGCS would alter reproductive decisions* *- Perceived chance of a carrier finding*
		Deliberation and informed choice	Outcomes related to making an informed choice to undertake RGCS	*- Deliberation on the decision to accept or decline testing* *- Informed choice (congruence of attitudes, knowledge, and test uptake)*
		Knowledge and understanding	Outcomes related to knowledge, incorporating concepts of understanding, recall and retention.	*- Knowledge before and after pre-test genetic counselling* *- Recall of correct screening result at a later timepoint*
	Delivery of care	Uptake of services	Outcomes related to actual or intention to uptake an offer of RGCS	*- Uptake of RGCS* *- Intention to accept the offer of RGCS*

		Barriers, facilitators, and factors influencing patient experience	Outcomes related to reasons for and against uptake of services, including offers of RGCS and further testing, as well as factors that influence experience of these services	*- Reasons for accepting/declining an offer of RGCS* *- Reasons or factors related to emotional reactions and psychological wellbeing* *- Sources of additional information used for decision-making regarding uptake of RGCS*
		Genetic counselling resource use	Outcomes related to the use and conduct of genetic counselling services	*- Number of post-test genetic counselling consultations* *- Time required for pre-test genetic counselling session*
		Goals of pre- and post-test genetic counselling	Outcomes related to the patient experience of pre- and post-test interactions with their health providers, and whether needs are met by their providers	*- Genetic counselling supported informed decision-making* *- Timing and method of information provision promoted understanding*
		Patient preferences	Outcomes related to patient preferences regarding the offer of RGCS	*- Preference regarding individual or couple-based results* *- Preference regarding conditions included in RGCS*
		Patient satisfaction with the processes of RGCS	Outcomes related to patient satisfaction with services provided during RGCS	*- Satisfaction with pre-test genetic counselling* *- Satisfaction with accessibility, cost and convenience of the screening process*
		Timeliness	Outcomes related to the timeliness of delivery of care in RGCS programs	*- Mean gestational age at time of reproductive carrier screening* *- Offer of reproductive carrier screening to women before 10 weeks gestation*
	Emotional functioning/ wellbeing	Decision satisfaction and regret	Outcomes related to decisional satisfaction or regret at a later timepoint	*- Retrospective satisfaction with the decision to have RGCS* *- Regret related to reproductive decision-making at a later timepoint*
		Psychological wellbeing	Outcomes related to the psychological impact of RGCS	*- Anxiety (measured at a range of timepoints)* *- Grief and loss (perception of pregnancy journey and expected future)*
	Perceived health status	Perception of personal health status after RGCS	Outcomes related to the impact of RGCS on perception of personal health	*- Impact of results on perception of own health*

	Personal circumstances	Decision-making (non-reproductive)	Outcomes related to the impact of results on decisions other than reproductive planning	*- Decisions regarding long-term care, disability, or life insurance* *- Lifestyle changes*
		Decision-making (reproductive)	Outcomes related to impact of results on decision-making for reproductive planning, including perceived or actual impact on these decisions	*- Pursued or planned to pursue alternate reproductive options* *- Intended reproductive decisions if identified as an increased risk couple*
		Familial implications	Outcomes related to the impact of results of patient relationships	*- Impact of results on couple's relationship* *- Number of heterozygotes that informed family members of their results*
		Perceived utility of RGCS	Outcomes related to patient's perceptions of the impact of RGCS and how they utilised the results	*- Confidence or empowerment related to reproductive decision-making* *- Results were available in a timely manner that allowed for consideration and decision-making*
	Social functioning	Acceptability of further testing or alternative reproductive options	Outcomes related to patients' perspectives, and wider societal perspectives, on prenatal diagnosis, termination of pregnancy, and preimplantation genetic diagnosis	*- Personal preferences regarding PND, PGD and TOP* *- Perception of societal acceptability of PND, PGD and TOP*
		Privacy concerns and stigmatisation	Outcomes related to the impact of results on privacy and stigmatisation	*- Concern regarding privacy or confidentiality* *- Concern regarding insurance*
Resource Use	Need for further intervention	Further testing	Outcomes related to the use of further testing for various purposes including clarifying reproductive risk as a couple, testing during a pregnancy, or electing PGD	*- Uptake of partner testing* *-Uptake of prenatal diagnosis in increased risk pregnancies at the time of screening* *- Uptake of preimplantation genetic diagnosis in increased risk couples*

The development of the CODECS outcome domains was an iterative process, initially compiled at the completion of the quantitative systematic review (Version 1.0 – Appendix A), reviewed and updated at the completion of the qualitative systematic review (Version 1.1 – Appendix B), and at the completion of the qualitative interview study (Version 1.2 – Appendix C).

Version 1.2 – defined at completion of the qualitative interview study. Documented updates to CODECS domains below, with 24 outcome domains remaining:
Domain changes: "Practice guidelines and recommendations" removed (deemed no longer applicable, only contained one outcome related to outdated practice recommendations)

Supplementary material C.7: Interview schedule

Welcome, introductions and explanation	
5 minutes	**Welcome** Introduce moderator and note taker. Thank you for speaking with me today, I appreciate you taking the time. My name is Ebony and I'm a genetic counsellor currently completing a PhD and this interview is part of an overarching study looking at the impact of carrier screening on patients such as yourself who accessed this testing. **Pre-amble:** As researchers, we do this by defining what we call 'outcomes', which is essentially something measurable that captures an aspect of your experience. I'll give you a detailed example of an outcome later in the interview. Our goal is to define 5-10 outcomes that when looked at all together give a good overall picture of your experience of carrier screening, which can then guide what researchers measure in the future. To start, I'm going to ask you to answer some broad questions that relate to your experience of carrier screening and then do an exercise where you think of some words that capture what it was like for you to have carrier screening. From this discussion together we'll come up with outcomes that relate to the words you use to describe your experience. This interview will last for up to an hour. I'll be video and audio recording the interview for our analysis and will store the recording securely for use in future research. If at any time you would prefer not to answer a question that is fine. If you want to take a break or do not feel comfortable, please let me know. Our discussion will be strictly confidential and you will not be identified in our results. We have ethics approval for this study. Did you have any questions for me before I start the recording [*if yes, address question]*. Once I start the recording I'm going to ask you for your consent to proceed and then we'll get started. [*start recording*] Thank you once again for agreeing to participate. I'll get you to indicate your verbal consent and we'll start.
Part 1: Exploratory Questions	
10 minutes	**Firstly, I need to ask for some quick demographic information. We use this to give some context around your answers:** 1. How old are you? 2. What is your highest level of education? 3. What is your ethnic background? 4. Do you have any family history of a genetic condition? **Can you tell me how you found out about carrier screening and why you decided to have this test?** Prompts [*if needed*]*:* 1. Tell me about your results? 2. How did you feel throughout the process? 3. Is there anything you felt was particularly good or bad about having carrier screening?

Part 2: Adapted Nominal Group Technique – Word Association Exercise	
20 minutes	The rest of the session is going to be quite interactive. We are going to do a word association exercise, and what I want you to do is always keep your experience of carrier screening that we've just discussed at the forefront of your mind. I'm going to break up the process of carrier screening into four time periods for us to think about: 1. Before testing 2. Waiting for your results 3. Receiving your results and the immediate time following that 4. Now, looking back on the experience so far and summing it up as a whole I'm going to prompt you to think about what was happening during each of these time periods and get you to take a few moments to write down some words that come to mind to sum it up. We'll then use the words that you come up with to decide on an outcome that they relate to. You can write down single words, or a short string of words, and try to aim for at least three but you can write down as many as you feel like.
	1| Firstly, think about the time leading up to carrier screening, when you spoke to your health care provider and decided to have this test. You might want to think about what information you were given, what your motivations were, and how you were feeling at that time. Write down some words that come to mind.
	2| Next, think about the period of time while you were waiting for your results, what was that like for you, how were you feeling, and write down some more words.
	3| Next, think about when you got your results, which might have been a phone call or at a doctors appt. Think about the information you were given, how were you feeling, think about what those results meant for you and what you had to do next. Pick a few words that sum up that time.
	4| Lastly, think about your perspective now, the bigger picture as you are looking back at the experience. Write down a few words that sum up your feelings overall about carrier screening and the impact it has had on you.
	Prompts [*if participant needs help thinking of words*]: • How did the testing impact on you personally, on you and your partner as a couple, or your family more broadly? • How did you feel throughout the process? • What did you understand about the test? • How did the timing of testing work for you? Did you feel like you had time to make decisions? • How supported did you feel? • How worthwhile was the test and why? • What were the benefits and/or harms, if any?
Break	

5 minutes	We have time for a short break now if you'd like [*check if they would like a break*] If yes, please don't leave the meeting but feel free to turn your cameras and microphones off and come back online in 5 minutes [*tell them what time to come back*]
Part 3: Adapted Nominal Group Technique – Eliciting Outcomes	

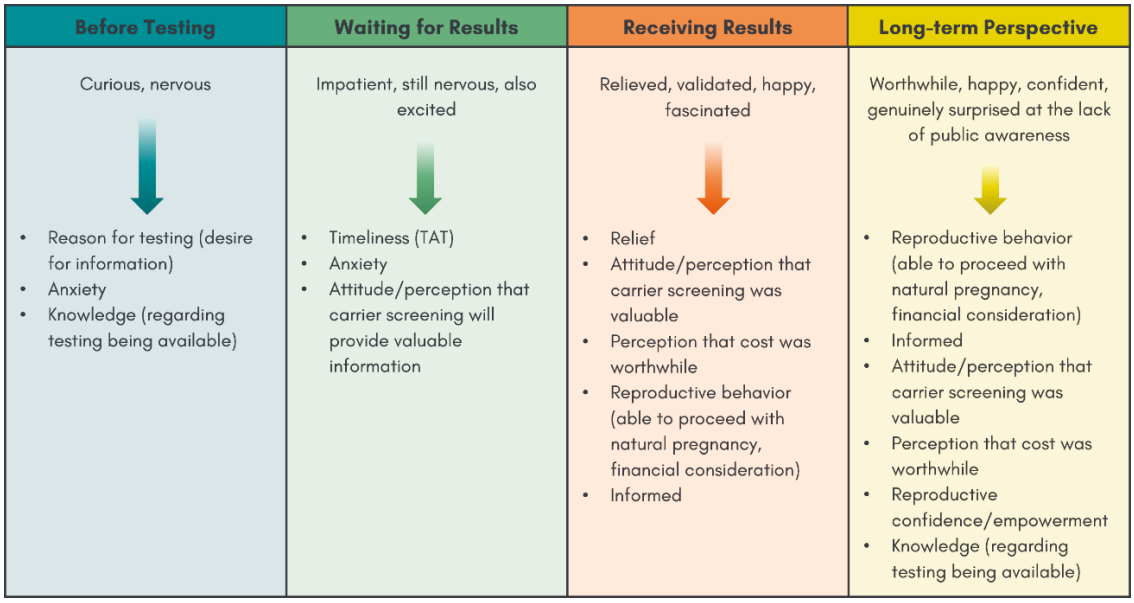
20 minutes	Now I'm going to use this online whiteboard to write down the words that you've chosen and then we'll discuss each of them to get some context around that word and think about a research outcome that it relates to. I'm going to give you an example of what an outcome is now since this is not an intuitive way that we usually think about things. Take COVID-19 as an example. If a researcher wanted to find out what impact the pandemic has had on people, they could look at a variety of different outcomes, they might look at:
	• People's mental health by measuring levels of depression, in that case the outcome being looked at would be depression. You could also look at different mental health outcomes like anxiety for example.
	  o Depression
	  o Anxiety
	• How people changed their behaviour, like wearing a mask.
	  o Uptake of wearing a mask in public
	• How informed people felt. One way to measure this would be to ask if people were satisfied with the information that was available about COVID; satisfaction with information provision. Or you could measure their understanding, by asking questions about COVID and seeing how many they get right; Knowledge about COVID.
	  o Satisfaction with information provision
	  o Knowledge about COVID
	If you were to look at all of these outcomes across a number of people, you would start to capture a broad picture of the experience of the pandemic, and this is what we want to do for carrier screening. Does that make sense? Any questions?

	Let's look at the first time-frame. Can you tell me what words you wrote down when thinking about the time before you had testing and when you were deciding to have it [*write down words on the whiteboard*]
	Can you give me a bit of context around this word? *[through discussion, associate the word with an outcome]* [*Repeat for all words*]
	Do you think that this outcome that I've written down captures your meaning? *[adjust as needed]* [*repeat for all time-frames*] • Tell me what words you wrote down when thinking about waiting for your results • Tell me what words you wrote down when thinking about receiving your results and the immediate time afterwards • *[if two-step screening]* Tell me what words you wrote down when thinking about waiting for your partners results • *[if two-step screening]* Tell me what words you wrote down when thinking about receiving for your partners results

	• Tell me what words you wrote down when thinking from your perspective now, some words that sum up your feelings about carrier screening now looking back on the experience
Part 4: Adapted Nominal Group Technique – Prioritising Outcomes	
	Now we are going to consider all the outcomes we have and think about which of these you think would be the most important for researchers to capture from your perspective as someone who has had reproductive carrier screening. If you can pick three that you think are the most important and consider why you made that choice. Take a few moments now to pick your top 3.
	Can you tell me what your number 1 most important outcome was and why? *[repeat with second and third ranked outcomes]* Prompts: Why do you think you ranked [outcome] high? Do you think that other people would also rank [outcome] high?
Summary & Conclusion	
5 minutes	Provide an overall summary of the session: 1. Do you feel that that is an adequate summary of what we discussed? 2. Have I missed anything or is there anything else anyone would like to add? 3. I'd like to ask for your feedback on the experience on this interview and if you have any specific feedback regarding the word association exercise? If you know anyone who would be interested, please pass on the details of the survey [*send f/u email with link to survey if they want to snowball*] Inform about Delphi and obtain to consent to contact them to participate. We'll end the session there, thank you again for your time and have a good night/day.

Supplementary material C.8: Example virtual whiteboard

Words generated during the word association exercise are recorded at the top, then through discussion are converted into research outcomes below.



Supplementary Material C.9 – Methodological feedback from participants

Participant feedback on the interview methodology was analysed thematically, with a focus on the word association exercise, in order to evaluate the effectiveness of this method for future studies wishing to incorporate qualitative methods in the development of a core outcome set.

Participant feedback on word association methodology for outcome conceptualisation

Feedback was available from nine of the fifteen participants and reflected a positive response regarding the word association exercise and its usefulness for conceptualising the unfamiliar concept of outcomes. Participants felt that the process was collaborative and gave them the opportunity to express outcomes in their own words.

> *"I think it was, you know, it was good because instead of you maybe putting words in my mouth it was, you know, very much collaborating because I was giving you the words and then we were piecing them together. So yeah, like I quite liked it."* – ID-4, low risk couple, proactive testing in the preconceptions setting, Australia

Participants noted that the word association exercise drew out information that may not have been possible from a narrative approach alone.

> *"I actually thought it was super smart, the way you primed the question and to think of feelings kind of in word blocks. I don't know that if you would have asked me in kind of a narrative question style if I would have distilled the same information. So, for me, I found it helpful to be able to kind of communicate my true feelings in more of a succinct way."* – ID-6, increased risk couple, RGCS following fetal loss, US

Participants felt that the nominal group technique of writing down words on their own before sharing them with the interviewer was a valuable component. They also felt that the virtual whiteboard was a good co-design tool for collaboration and ensuring that the recorded outcomes were reflective of both the patient and interviewers' perspectives.

> "*I think it was good I, I think had it just been dialogue I maybe wouldn't have thought about all of the factors that we talked about. I think it was good for me to write it down on my own and then for you to share your screen with me. I think it was really helpful to make sure we were on the same page.*" – ID-9, increased risk couple, RGCS following fetal loss, Canada

One participant noted that a lot of information could be drawn out from only a few words.

> *"You definitely drew more information out of me from those words, because I couldn't really think of much, like here are 2 words, and you managed to draw so much more from that. So I'd say it's good."* – ID-10, low risk couple, proactive RGCS in the preconception setting, Australia

One participant commented on how the word association exercise helped them to gain confidence as they proceeded through the interview.

> *"The further we got along, I got more confident to share the emotions and then I think I felt more, I felt like a lot of ease as we got along and more and more ideas started popping out."* – ID-11, low risk couple, proactive testing in the preconception setting, Australia

One participant commented on the structured approach to the interview, from broad to specific aspects, and how this facilitated greater insight.

> *"I think it definitely is a really good way compared to just asking 'what do you think about carrier screening'... the logical structured way that you provided the interview, I think is really, really helpful and I think it helps to elicit really insightful responses compared to just asking open ended questions."* - ID-11, low risk couple, proactive testing in the preconception setting, Australia

Limitations of patient feedback

Participants were asked for feedback at the conclusion of the interview and there is a chance that they would not have felt comfortable providing negative feedback directly to the interviewer. Of the 6 participants that we did not have feedback data for, 5 of these were from the first 3 interviews before we started asking for feedback, and one declined to give feedback.

Appendix D – Supporting information for Chapter 6

Summary of Content

Supplementary material D.1: Protocol changes for the AUS/NZ Delphi process and implications for an international Delphi process

Stage	Original protocol	Changes	Implications
Developing the survey	*"The preliminary list of outcomes generated from the previous steps will be reviewed by the research team to form the basis of the Delphi survey"*	No changes were made to the process of compiling outcomes and developing the survey	None
Sample size	*"We will aim to recruit at a minimum 50 patient participants and 50 participants from other professional stakeholder groups to the first round of the Delphi survey"*	We recruited 10% of the original planned sample size of 100 international participants, aiming for 10-15 Australian/New Zealand participants	Increased sample size with broad international representation is needed
Participants	*"Five key stakeholder groups with current or recent personal, clinical, research, or policy experience of RGCS will be targeted for the Delphi survey: patients (including both carriers and non-carriers identified through targeted or expanded screening), genetic health professionals (genetic counsellors and clinical geneticists), non-genetic health professionals (obstetrician/gynaecologists, midwives, general practitioners), researchers, and policymakers."*	Due to the reduction in planned sample size we elected to purposely sample professional participants whose expertise overlapped multiple categories (GHP, researcher and policy-maker sub-groups). These were considered a new 'expert HPs' group for the purpose of the pilot.	Inclusion of non-genetics health professionals is needed. Genetic health professional sub-groups will need to be explored in more detail to understand nuance between groups.
Recruitment	*"Patient participants from focus groups/interviews will be invited to participate in the Delphi process. We will also recruit through social media to reach our goal of 50 total patient participants; researchers will be purposively sampled based on first and last authors of papers included in our systematic reviews; genetic and non-genetic health professionals will be purposively sampled based on professional networks and member lists of relevant professional organisations; policy-makers will be purposively sampled from listed committee members on major practice recommendations related to RGCS. Participants who respond to expressions of interest will be directed to an online survey to confirm their eligibility."*	We did not recruit via social media as there were sufficient patients available from our qualitative interviews cohort to make up our 50% planned representation. Expert HPs were recruited as previously planned. The eligibility survey was determined not to be needed for the pilot due to the purposive sampling approach.	A more extensive recruitment process will be needed to reach the sample size needed for an international Delphi. Implementation of an eligibility survey will be needed as the sampling will not be as direct and purposive as the pilot.

Data collection	*"In round 1, participants will be asked to rate each outcome on a 9-point Likert scale…rating 1 to 3 will be interpreted as 'limited importance', 4 to 6 as 'important, but not critical', and 7 to 9 as 'critical importance'. An option of 'unsure' will also be available…the sequence of questions will be randomised to minimise ordering bias"*	The 'unsure' option was not included as we needed all participants to provide a response due to the small sample size. We did not randomise the order of questions.	Consideration should be given to including the 'unsure' option and whether to randomise items.
Criteria for inclusion/ exclusion in subsequent rounds	*"Criteria for inclusion in round 2 will be any outcomes that are rated 7 to 9 (critically important) by >50% of participants and 1 to 3 (limited importance) by no more than 15% of any single stakeholder group"*	Due to the small sample size, this approach was no longer appropriate as 15% percent equated to 1 participant. Hence, the opinion of 1 participant that an outcome was of limited importance could lead to its exclusion. The alternative approach chosen is outlined in full in Chapter 6.	The approach used in this pilot is scalable. The benefits of carrying this over, versus reverting to the previously defined criteria should be reviewed and decided on prior to commencement of the international Delphi.
Displaying results of Round 1	*"Results will be presented graphically to participants at the time of the second round of the survey along with their rating of each outcome and any representative comments provided by participants that indicate their reasoning. This will allow participants to compare their ratings to other participants and consider whether they would change their rating in the next round."*	The Qualtrics platform did not have an easy way to link participants previous responses, necessitating the display of Round 1 rankings in a tabulated form with participants given a study ID to identify their rankings within the table.	The use of a table to display Round 1 rankings will not be feasible in a larger Delphi. An alternative platform, that links participant responses across rounds will be needed.
Duration	*"Each round of the survey will be open for a minimum of 4 weeks to provide participants with sufficient time to complete it. A maximum of 3 reminders will be sent to participants when 2 weeks, 1 week, and 1 day are remaining to complete the survey."*	The planned protocol determined a period of 4-weeks for participants to complete the Delphi, this was extended to 6 weeks for the pilot since the small sample size did not allow for high rates of attrition.	The larger sample size planned for an international Delphi may allow for shorter time periods for each round.
Data analysis	*"We will summarise the overall distribution in ratings for outcomes across the rounds of the Delphi survey and the points at which outcomes were excluded from consideration. The mean and median will be calculated for each outcome. Data will be analysed in sub-groups to allow comparison between prioritisation of outcomes between health consumer participants and other stakeholder participants, and also between different subsets of the other stakeholder groups (for example, genetic health professionals versus non-genetic health professionals)."*	Distribution of rankings, mean and median were calculated as planned. Due to the small sample size, sub-group analysis and difference between groups was not able to be determined.	Sub-group analysis of an international Delphi will provide much needed insights to understand different opinions between groups.

Supplementary material D.2: Email invitations

Email invitation to health consumers

These participants have participated in a focus group or interview and therefore have prior knowledge of the overarching study. They are already known to be eligible based on their prior participation and will simply need to respond to the email to be sent the link to the survey.

Hi [insert name],

We are contacting you because you recently participated in an interview with our research team about your experience of reproductive carrier screening. At the end of your participation, you were asked if you were willing to be contacted about future stages of this project, and you indicated that you were.

We are now conducting an online survey as the next step of our research. This survey may be different to other online surveys that you have participated in in the past. It will ask you to read about an outcome, which you might remember is any measurable effect of a test, and think about how important this outcome is to you. This survey is designed to rank which outcomes are really important to patients so that future research can be sure to measure and report these outcomes. The survey is also going to be completed by doctors and other health professionals that offer reproductive carrier screening so that we can see what outcomes are important to them too.

This type of survey is called a Delphi survey, and involves 2 to 3 rounds of this type of ranking. This means you will be asked to complete 2 or 3 online surveys, each taking 30 minutes to an hour. Each round of the survey is expected to get a bit shorter and be a bit quicker to complete. The surveys will be spaced out over 4-6 months commencing January 2022. Each will be open for at least 4 weeks to give you plenty of time to complete it. It is really important for us to have all the online surveys completed, so if you have any concerns about being able to complete 2 or 3 surveys, please contact us.

If you are interested in participating, you can simply reply to this email and we will send you a link to further information and the first online survey when it launches in January.

Thank you for considering participating in this next step for our research. Remember you can always contact us if you have any questions.

Kind regards,

Ebony Richardson
Lead Investigator
Core Outcome Development for Carrier Screening (CODECS) Study
e: ebony.j.richardson@student.uts.edu.au

Email invitation to purposively sampled members from other stakeholder groups (clinicians, researchers, policy-makers)

Recipients of this email will be purposively sampled stakeholders, and any colleagues that they snowball out to. Interested recipients will click on a link that will take them to the participant information sheet and a short demographic/eligibility survey. Once participants fill out the short online survey indicating that they would like to participate, their responses will be checked for eligibility. All eligible participants will then be sent the link to the Delphi survey.

Dear [insert name],

The Core Outcome Development for Carrier Screening (CODECS) study is an initiative being undertaken by Ebony Richardson in the course of her PhD candidature at the University of Technology Sydney. This study aims to identify which outcomes of reproductive carrier screening are important to patients, clinicians, researchers and policy-makers to inform the development of a Core Outcome Set (COS).

Core outcome sets are an emerging means of ensuring methodological rigor in medical research and reducing research waste. In the area of reproductive carrier screening, a large body of literature exists, but there is a high degree of heterogeneity in what outcomes are assessed and how they are measured. This has created difficulty in conclusively demonstrating benefits and harms of reproductive carrier screening as a health intervention.

There are three main reasons we are conducting this study:

- Research that doesn't assess outcomes that are relevant to end-users is limited in its application to inform practice decisions.
- Without consistency across what outcomes are being measured, we cannot compare the effects of an interventions between studies
- Resources are wasted when outcomes are measured and reported inconsistently.

Establishing a core outcome set can help to ensure that studies on reproductive carrier screening report outcomes that are important and relevant to you.

You are invited to participate in the CODECS Delphi panel to achieve consensus (agreement) on the most important outcomes that should be included in the core outcome set for reproductive carrier screening. This involves completing a Delphi survey, which includes two to three rounds spaced out over 4-6 months commencing January 2022. Each survey should take approximately 30 minutes to an hour to complete, and will be open for at least 4 weeks to allow plenty of time for completion. It is really important for us to have participants complete all surveys, so if you have any concerns about being able to complete 2 or 3 surveys, please contact us.

If you are interested in participating, you can simply reply to this email and we will send you a link to further information and the first online survey when it launches in January.

If you are unable to participate, we would appreciate suggestions of colleagues that you believe would be suitable to participate in this Delphi survey for us to approach.

Please contact us if you have any questions regarding this study.

Kind regards,

Ebony Richardson
Lead Investigator
Core Outcome Development for Carrier Screening (CODECS) Study

CODECS Steering Committee | Ebony Richardson, Dr Chris Jacobs, A/Prof Alison McEwen, A/Prof Toby Newton-John

e: ebony.richardson@uts.edu.au

Email with link to Delphi survey for all participants

Recipients of this email will have been deemed eligible to participate after completing the demographic/eligibility survey. This email will provide them with a personalised link to complete the survey online.

Thank you for your interest in taking part in this Delphi Survey. The aim of the survey is to find out what effects of testing (also known as outcomes) are important and relevant to patients undertaking reproductive carrier screening, and health professionals involved in their care.

You will be asked to rate the importance of [insert number] outcomes based on your opinion about how important you think they are for people who are undertaking reproductive carrier screening. There is no right or wrong answers. The outcomes have been collected from a review of published studies and research with patients. You will be able to add outcomes and rank those too.

A copy of the Participant Information is available [insert link]

The survey is voluntary. All participants who complete the survey will receive a copy of the results.

Click on the following link to begin the survey: {insert link] Please do not forward this link as this is unique to you.

Thank you in advance for your participation.

Supplementary material D.3: Participant information sheet

UTS HREC Reference No: ETH20-5179

The CODECS Study: Delphi Process for Development of a Core Outcome Set for Reproductive Genetic Carrier Screening

WHO IS DOING THE RESEARCH?

My name is Ebony Richardson and I am a student at UTS. My supervisor is Dr Chris Jacobs, who can be contacted at chris.jacobs@uts.edu.au

WHAT IS THIS RESEARCH ABOUT?

This research is to find out about outcomes that are important for all key stakeholders in reproductive genetic carrier screening. A stakeholder is any person that has a vested interest in reproductive genetic carrier screening and may include patients, clinicians, researchers and policy-makers.

In healthcare, when a new type of test becomes available we need evidence about its benefits and harms to make decisions about whether to offer this test to our patients. Evidence is gathered by researchers who look at the effect of the new test on the patient by measuring 'outcomes'. An outcome is any measurable effect of the test. For example, an outcome of a genetic test might include:

- Detection of a genetic variant, or mutation, that is known to cause disease or increase risk of disease
- Psychological harms, such as increased anxiety caused by the testing process or test result
- Behaviour change, such as deciding to have invasive testing during a pregnancy

We have conducted prior research to develop a long list of outcomes that have been previously measured in research on reproductive genetic carrier screening or have been suggested as part of qualitative research with patients. The purpose of this online survey is to determine the degree of consensus on which outcomes should be included in a 'core outcome set', which is a set of outcomes that should be measured in all research on reproductive genetic carrier screening.

WHY HAVE I BEEN ASKED?

You have been invited to participate in this study because you are part of one of the key stakeholder groups:

- Patients who have had reproductive genetic carrier screening as part of their pregnancy health care or in planning for future pregnancies.
- Genetic health professionals, including genetic counsellors and clinical geneticists, that are recently or currently involved in offering reproductive genetic carrier screening to patients or managing their results.
- Non-genetic health professional, including maternal fetal specialists, midwives, and general practitioners, that are recently or currently involved in offering reproductive genetic carrier screening to patients or managing their results.
- Researchers that are recently or currently involved in undertaking research on reproductive genetic carrier screening
- Policy-maker that are recently or currently involved in the creation of practice recommendations, policy, or guidelines related to reproductive genetic carrier screening.

IF I SAY YES, WHAT WILL IT INVOLVE?

If you decide to participate, you will be asked to complete 2-3 online surveys over the next 4-6 months.

The online survey method is called a Delphi survey. This is a specific method that will ask you to rank the importance of each outcome that we have identified in our prior research. It involves completion of 2 to 3 surveys spread over a number of months.

In the first survey, you will be provided with a definition and example of an outcome and asked to provide a ranking of how important you believe it to be. You will also have the opportunity to comment on the outcome, suggest changes to the definition, or suggest new outcomes that you think are missing from the survey. The first survey is anticipated to take approximately 30 minutes to an hour to complete and will be open to respond to for at least 4 weeks. The results of the first survey will be used to exclude any outcomes that were agreed by the majority of participants to be unimportant.

At the start of the second survey you will receive feedback about the ranking of outcomes from all participants in the first round, allowing you to see how your opinion is placed amongst the wider group. You will then be asked to go through again and re-rank the outcomes and make comments on the definitions. You are not obligated to change your ranking based on the answers of other participants, but are encouraged to read the comments provided about why outcomes were given a particular rating and determine if this would change your mind about your rating. The second survey is anticipated to take approximately 30 minutes to an hour to complete and will be open to respond to for at least 4 weeks.

If there is sufficient agreement at the end of the second survey, we will stop there and proceed to analyse our results. However, if there is still a lack of agreement we will continue to a third survey which will follow the same structure as the second.

ARE THERE ANY RISKS/INCONVENIENCE?

Yes, there are some risks/inconvenience. You may experience some inconvenience given the duration of this research over a number of months. We have made efforts to minimise the time required for participation, however please contact us if you have any concerns.

DO I HAVE TO SAY YES?

Participation in this study is voluntary. It is completely up to you whether or not you decide to take part.

WHAT WILL HAPPEN IF I SAY NO?

If you decide not to participate, it will not affect your relationship with the researchers or the University of Technology Sydney. If you wish to withdraw from the study once it has started, you can do so at any time without having to give a reason, by contacting Ebony Richardson at ebony.j.richardson@student.uts.edu.au

However, it may not be possible to withdraw your data from the study results if these have already had your identifying details removed.

If you decide to leave the research project, we will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected up to the time you withdraw will form part of the research project results.

CONFIDENTIALITY

By submitting the online survey you consent to the research team collecting and using personal information about you for the research project. All this information will be treated confidentially. Your information will be stored securely and will only be accessible to the primary researcher, Ebony Richardson, and my supervisor, Dr Chris Jacobs.

We would like to store your information for future use in research projects that are an extension of this research project. In all instances your information will be treated confidentially.

We plan to publish the results of this study in medical journals. In any publication, information will be provided in such a way that you cannot be identified.

WHAT IF I HAVE CONCERNS OR A COMPLAINT?

If you have concerns about the research that you think I or my supervisor can help you with, please feel free to contact us on chris.jacobs@uts.edu.au or ebony.j.richardson@student.uts.edu.au

You will be given a copy of this form to keep.

NOTE:
This study has been approved in line with the University of Technology Sydney Human Research Ethics Committee [UTS HREC] guidelines. If you have any concerns or complaints about any aspect of the conduct of this research, please contact the Ethics Secretariat on ph.: +61 2 9514 2478 or email: Research.Ethics@uts.edu.au], and quote the UTS HREC reference number. Any matter raised will be treated confidentially, investigated and you will be informed of the outcome.

Supplementary material D.4: Guidance for participants document – Round 1

What is an outcome?

An outcome is any measurable aspect of a health intervention.

What is an outcome domain?

An outcome domain is a group of outcomes that are similar or closely related to each other.

What is the CODECS study?

The Core Outcome Development for Carrier Screening (CODECS) study is a PhD project aimed at developing a core outcome set for reproductive genetic carrier screening (RGCS).

What is a core outcome set?

A core outcome set is a minimum set of outcomes that should be measured and reported in all studies on reproductive genetic carrier screening. To date, a systematic review of the research literature and interviews with patients who have accessed RGCS have allowed the development of a long list of outcomes to consider for inclusion in a core outcome set. The next step is to present the long list of outcomes to experts in RGCS, including patients, health professionals and researchers, and determine their opinions on the importance of each outcome. These opinions are collected through a Delphi survey.

What is a Delphi survey?

A Delphi survey is a type of survey that is conducted over multiple rounds, with each round being informed and developed based on participants answers in the preceding round. The goal of a Delphi is to understand how much agreement or 'consensus' there is between participants.

The first round of this Delphi survey aims to refine the long list of outcomes, and remove outcomes that are agreed by most participants to be of low importance. Outcomes that are agreed to be most important will be taken forward to the second round of the Delphi survey to be considered in greater detail.

How do I answer the questions?

The questions will ask you to think about the importance of an outcome, and rank this importance between 1 to 9, with 1 being the lowest importance and 9 being highest importance. Your ranking are grouped into 3 categories:

1-3 = limited importance (very few studies should report this outcome)
4-6 = important, but not critical (some, but not all, studies should report this outcome)
7-9 = critically important (**all** studies should report this outcome)

Consider the below example when deciding on the most important outcomes when evaluating flowers in a floristry competition:

1. Colour
Judges should assess which flower has the brightest colour

Limited importance	Important, but not critical	Critical importance
◯ 1 (low)	◯ 4 (low)	◯ 7 (low)
◯ 2 (medium)	◯ 5 (medium)	◯ 8 (medium)
◯ 3 (high)	◯ 6 (high)	◯ 9 (high)

Firstly, decide whether you think the outcome is limited importance, important but not critical, or critical importance.

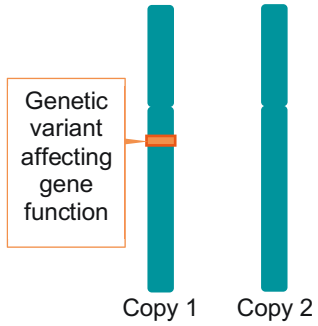
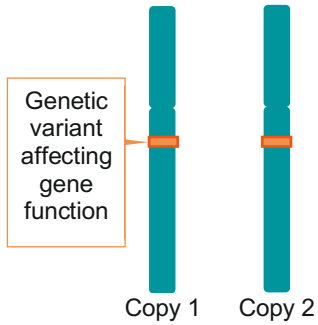
Secondly, within each category, decide whether you feel the outcome is of low, medium or high importance.

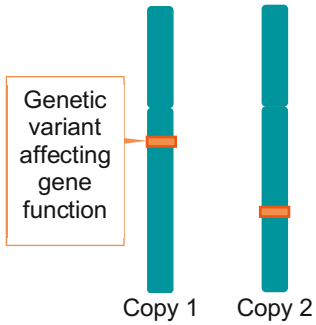
If you think that colour is critically important in assessing flower quality, but not the most important, you might select 7. This would indicate that it should be assessed by all judges but other outcomes, such as scent or petal shape, might be more important.

Abbreviations

CODECS	Core outcome development for carrier screening; the name of this research study
RGCS	Reproductive genetic carrier screening
COS	Core outcome set
PND	Prenatal diagnosis, including chorionic villus sampling (CVS) and amniocentesis
IVF/PGD	In vitro fertilisation with pre-implantation genetic diagnosis
TOP	Termination of pregnancy
CVS	Chorionic villus sampling

Definitions

Heterozygous	We all have two copies of each of our genes, one from each parent. Heterozygous refers to variants or mutations affecting one copy of a gene, while the other gene is unaffected. Heterozygous carriers can include carriers for recessive conditions, or female carriers of X-linked conditions (see below).	
Homozygous	We all have two copies of each of our genes, one from each parent. Homozygous refers to a variant or mutation that affects both copies of a gene, and is located in the same spot on both copies. In recessive conditions, homozygous individuals will be affected. In X-linked conditions, females with both copies of their X chromosome effected will be affected.	

Compound Heterozygous	We all have two copies of each of our genes, one from each parent. Compound heterozygous refers to a variant or mutation that affects both copies of a gene, but the variants are not located in the same spot on both copies. This has the same effect as a homozygous variant.	
Hemizygous	This term is used in regards to the sex chromosomes, with males having XY chromosomes. Hemizygous refers to men who have a genetic variant on the single copy of their X chromosome. For an X-linked condition, this would indicate that that male is affected.	
Recessive conditions	These are conditions where both copies of a gene must have a genetic variant affecting its function in order to cause disease (homozygous or compound heterozygous). Heterozygous individuals are considered carriers and are only at increased risk of having an affected child if their partner is also a carrier of a genetic variant on the same gene.	
X-linked conditions	These are conditions caused by genetic variants on the X chromosome.	
Chorionic villus sampling (CVS)	This is a medical procedure performed in pregnancy to take a sample of the placenta to test for genetic conditions in increased risk pregnancies.	
Amniocentesis	This is a medical procedure performed in pregnancy to take a sample of the amniotic fluid to test for genetic conditions in increased risk pregnancies.	
Genetic counselling	For the purpose of this study, genetic counselling is considered a process that can be performed by a range of health professionals including GPs, midwives, OBGYNs and maternal fetal medicine specialists, as well as specially trained genetic health professionals such as genetic counsellors and clinical geneticists.	

If you have any questions that are not addressed here, do not hesitate to contact me at **ebony.richardson@uts.edu.au**

Supplementary material D.5: Round 1 Delphi survey

Introduction to CODECS Study Delphi Survey

Thank you for agreeing to take part in the Core Outcome Development for Carrier Screening (CODECS) Delphi Survey.

Key definitions and answers to common questions to assist you in completing this survey can be found [link to Guidance for Participants], we encourage you to download this document and keep it nearby as you work through the survey.

What is a Delphi survey?

A Delphi is a type of survey that is conducted across multiple rounds, each of which is developed and informed by your responses in the round before. This is the first round of an Australian and New Zealand Delphi survey that will inform an international Delphi survey in the future.

The goal of a Delphi survey is to understand how much agreement or 'consensus' exists across the participants on outcomes that should be measured and reported in studies of reproductive genetic carrier screening (RGCS). Your opinion will inform the development of a core outcome set.

What is a core outcome set?

A core outcome set is a list of key outcomes that have been agreed through consultation with patients and health professionals to be the minimum that should be measured and reported in **all** studies on RGCS. A core outcome set should include outcomes that are able to capture the impact of RGCS and inform recommendations for how RGCS should be offered in practice. Studies may measure other outcomes as well, however the core outcomes should always be reported so that they can be compared and combined across studies. Therefore as you are considering your responses to each outcome proposed in this survey, consider how important you think it is that this outcome is reported by all studies (critically important), some studies (important, but not critical), or very few studies (limited importance).

What is involved?

This survey will involve completing 2 rounds from January to April 2022, with a possible 3rd round in May 2022 if needed. Each round will be open for 4 weeks. This first round is expected to take approximately an hour of your time to complete; subsequent rounds are anticipated to be less time intensive. At the end of this process we will understand which outcomes are most important to consider for inclusion in the core outcome set. It is important to complete all rounds of the survey. You can elect to receive a report of the final results if you complete all surveys.

For more information please read the **Participant information sheet**

This study has received Ethics approval from The University of Technology Sydney Ethics Committee (UTS HREC ETH20-5179)

By clicking on the 'Next' button below, you are indicating that you understand that the data that you provide in this survey will be collected and retained by researchers from the University of Technology Sydney. If you do not wish to continue to the Delphi survey, please close your browser window to exit the survey.

Please provide your name and title

_____

Please indicate if you would like to be acknowledged by name in any publications stemming from this survey

○ Yes, please acknowledge me using the name and title provided above

○ No, I would prefer to stay anonymous in any publications

Please select the below group that applies to you. You may select multiple options if appropriate (e.g. if you are a genetics health professional also involved in developing policy)

- ❍ Patient who has had reproductive genetic carrier screening
- ❍ Genetic health professional (genetic counsellors and clinical geneticists)
- ❍ Non-genetics health professional (OBGYN and maternal fetal medicine specialist)
- ❍ Researcher previously or currently involved in a study evaluating reproductive genetic carrier screening
- ❍ Policy-maker that has contributed to guidelines or recommendations regarding reproductive genetic carrier screening
- ❍ Other (please specify)
  _____

Outcomes Ranking

Please read these instructions carefully as they will ensure that you have all the information needed to complete the survey.

There are **21** groups of outcomes (known as outcome domains) to consider in this survey.

The outcomes that you will be ranking have been developed from:

- A comprehensive review of outcomes that have been previously reported in studies on RGCS. These include quantitative studies (database audits and surveys) and qualitative studies (interviews or focus groups with patients); and
- Outcomes that have been identified by patients in qualitative interviews conducted as part of the CODECS study

This long list of outcomes represents all the outcomes that have been assessed by researchers to date, therefore there is a wide range of importance that will be represented in this first round of the Delphi survey. Your responses will allow us to refine this list and reduce it to a smaller number of outcomes to consider in greater depth in the second round of the Delphi survey.

We would like you to review each outcome and rate its importance on a scale of 1 to 9, with 1 being the lowest importance and 9 being the highest importance. If you would like to provide a comment or clarify the reason behind your rating, please do so in the box provided. Providing a reason or comment in the box is optional and does not need to be completed for each question.

Please enter a rating for all outcomes. The outcomes are in no particular order. There are no right or wrong responses. We are interested in your opinion.

There may be outcomes not otherwise listed that you think should be included in our list. If you would like to add any additional outcomes, please include these in the box provided and indicate a ranking from 1 to 9 that you would give each.

Your participation is voluntary. You may exit the survey at any time and your progress will be saved. You can return to complete the survey at a later time by using the same personalised link. You can see your progress through the survey indicated by the progress bar at the top of your screen. By clicking submit at the end of the survey you are consenting for your data to be used for research purposes.

Please contact ebony.richardson@uts.edu.au if you encounter any issues or require assistance with completing the survey.

Domain 1 Primary Laboratory Outcomes There are 2 outcomes to consider in this outcome domain.	**Limited importance**			**Important, but not critical**			**Critically important**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1. Carrier detection rate Studies should report the number of heterozygous carriers identified.	❍	❍	❍	❍	❍	❍	❍	❍	❍
2. Identification of increased risk couples Studies should report the number of increased risk couples identified (defined as both members of a reproductive couple being carriers of the same recessive condition, or the female member being a carrier of an X-linked condition).	❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments
(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

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_____

Additional outcomes to suggest
(You can add suggestions for additional outcomes here or at the end of the survey)

_____
_____

Domain 2 Secondary and Incidental Laboratory Outcomes There are 2 outcomes to consider in this outcome domain.	**Limited importance**			**Important, but not critical**			**Critically important**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1. Identification of results which indicate the prospective parent undertaking RGCS is at increased risk or affected with one of the conditions screened Studies should report the number of homozygous, hemizygous or compound heterozygous individuals identified through RGCS.	❍	❍	❍	❍	❍	❍	❍	❍	❍
2. Identification of variants where the association with disease risk is unclear Studies should report the number of variants of uncertain significance identified through RGCS.	❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments
(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

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_____

Additional outcomes to suggest
(You can add suggestions for additional outcomes here or at the end of the survey)

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Domain 3 Technical Laboratory Outcomes There are 2 outcomes to consider in this outcome domain.	**Limited importance**			**Important, but not critical**			**Critically important**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1. Laboratory errors leading to the incorrect interpretation of results Studies should report the rate of laboratory errors (such as sample mix-ups or contamination of samples) that lead to the reporting of incorrect results. This includes false negatives (where the patient receives a negative result indicating they are NOT a carrier, however is later found to be a carrier), and false positives (where the patient receives a positive result indicating they are a carrier, however this is later found to be incorrect).	❍	❍	❍	❍	❍	❍	❍	❍	❍
2. Test failure and requests for replacement samples Studies should report the rate of test failure as a result of insufficient or poor-quality DNA.	❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments
(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

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Additional outcomes to suggest
(You can add suggestions for additional outcomes here or at the end of the survey)

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Domain 4 Uptake of Services There are 4 outcomes to consider in this outcome domain.	**Limited importance**			**Important, but not critical**			**Critically important**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1. Number of RGCS tests Studies should report the number of screening tests conducted.	❍	❍	❍	❍	❍	❍	❍	❍	❍
2. Uptake of RGCS Studies should report the number of patients offered RGCS that accept the offer and consent to screening.	❍	❍	❍	❍	❍	❍	❍	❍	❍
3. Decline of RGCS Studies should report the number of patients offered RGCS who decline the offer.	❍	❍	❍	❍	❍	❍	❍	❍	❍
4. Barriers and facilitators to access and uptake of RGCS Studies should report patient perception of the accessibility of RGCS and how this influences their decision to have it. Accessibility includes aspects such as cost and convenience of the process.	❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments
(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

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Additional outcomes to suggest
(You can add suggestions for additional outcomes here or at the end of the survey)

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Domain 5 Genetic Counselling Resource Use There are 4 outcomes to consider in this outcome domain. *For the purpose of this study, genetic counselling is considered a process that can be performed by a range of health professionals including GPs, midwives, OBGYNs and maternal fetal medicine specialists, as well as specially trained genetic health professionals such as genetic counsellors and clinical geneticists.*	**Limited importance**			**Important, but not critical**			**Critically important**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1. Uptake of pre-test genetic counselling Studies should report the number of patients that elect to discuss RGCS with their healthcare provider when offered.	❍	❍	❍	❍	❍	❍	❍	❍	❍
2**. Time required for pre-test genetic counselling** Studies should report the length of time taken to explain and consent a patient for RGCS.	❍	❍	❍	❍	❍	❍	❍	❍	❍
3. Uptake of post-test genetic counselling for increased risk couples For studies where RGCS is offered by a non-genetics health professional (GP, midwife or maternal fetal specialist), studies should report the number of increased risk couples that accepted an offer of post-test counselling with a genetic health professional (genetic counsellor or clinical geneticist).	❍	❍	❍	❍	❍	❍	❍	❍	❍
4. Mode of genetic counselling Studies should report the number of patients utilising face-to-face, telephone, or telehealth service.	❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments
(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

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Additional outcomes to suggest
(You can add suggestions for additional outcomes here or at the end of the survey)

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Domain 6 Further Testing and Reproductive Decision-Making There are 8 outcomes to consider in this outcome domain.	**Limited importance**			**Important, but not critical**			**Critically important**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1. Uptake of partner testing (in sequential screening) Sequential screening refers to studies where RGCS is offered to one reproductive partner first, and then partner testing offered if a carrier finding is returned. Studies should report the number of patients who elect to test their reproductive partner when they are found to be a carrier of a recessive condition.	❍	❍	❍	❍	❍	❍	❍	❍	❍
2. Barriers and facilitators to access and uptake of partner testing Studies should report the factors involved in decision-making to test a reproductive partner, including aspects such as cost and convenience of the process.	❍	❍	❍	❍	❍	❍	❍	❍	❍
3. Uptake of prenatal diagnosis Studies should report the number of patients that accept and decline prenatal diagnosis (CVS or amniocentesis) to determine the genetic status of an at-risk pregnancy following an increased risk result from RGCS.	❍	❍	❍	❍	❍	❍	❍	❍	❍
4. Barriers and facilitators to access and uptake of prenatal diagnosis Studies should report the factors involved in decision-making to have a CVS or amniocentesis following an increased risk RGCS results, including aspects such as risks associated with invasive procedures, and that they wouldn't terminate a pregnancy based on result based on cultural, moral, religious beliefs or the condition being treatable.	❍	❍	❍	❍	❍	❍	❍	❍	❍

5. Reproductive decisions following an increased risk result Studies should report the reproductive decisions made by patients based on RGCS, including the decision to continue or terminate a pregnancy determined to be affected through prenatal diagnosis, uptake of IVF with PGD in future pregnancies, decision to proceed with natural conception and test future pregnancies, the decision to not have children or have a smaller family than initially planned, use of an egg or sperm donor.	❍	❍	❍	❍	❍	❍	❍	❍	❍
6. Barriers and facilitators of patient uptake of IVF/PGD in increased risk couples Studies should report factors that influence uptake of IVF/PGD, including aspects such as access, cost, medicalisation of the pregnancy journey, and whether the patients are already having IVF or fertility issues.	❍	❍	❍	❍	❍	❍	❍	❍	❍
7. Barriers and facilitators of patients experience of PND, IVF/PGD and TOP Studies should report external factors such as the healthcare and social context that may impact patients undergoing PND, IVF/PGD and TOP, including aspects such as access to services and financial considerations.	❍	❍	❍	❍	❍	❍	❍	❍	❍
8. Support needs when making reproductive decisions Studies should report the number of patients that requested sources of additional information, such as support groups or connection with those with lived experience of a genetic condition, to inform their reproductive decisions.	❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments
(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

Additional outcomes to suggest
(You can add suggestions for additional outcomes here or at the end of the survey)

Domain 7 Pregnancy Outcomes There are 5 outcomes to consider in this outcome domain.	**Limited importance**			**Important, but not critical**			**Critically important**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1. Results of prenatal diagnosis (CVS or amniocentesis) Studies should report the number of affected pregnancies identified through prenatal diagnosis.	❍	❍	❍	❍	❍	❍	❍	❍	❍
2. Rate of fetal loss following prenatal diagnosis (CVS or amniocentesis) Studies should report the number of pregnancies that miscarried following prenatal diagnosis.	❍	❍	❍	❍	❍	❍	❍	❍	❍
3**. Decision to continue or terminate a pregnancy identified to be affected through prenatal diagnosis** Studies should report the number of affected pregnancies that were terminated following results of prenatal diagnosis.	❍	❍	❍	❍	❍	❍	❍	❍	❍
4. Birth rates for conditions that were included in screening Studies should report the number of babies born affected with a condition that was screened for. This may be because parents chose to proceed with a pregnancy known to be affected, may have been aware of increased risk but chose not to test during the pregnancy, or because of a laboratory error that missed identifying an increased risk.	❍	❍	❍	❍	❍	❍	❍	❍	❍
5. Results of IVF with preimplantation diagnosis (PGD) utilised by increased risk couples in subsequent pregnancies Studies should report the number of unaffected ongoing pregnancies following IVF with PGD.	❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments
(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

Additional outcomes to suggest
(You can add suggestions for additional outcomes here or at the end of the survey)

Domain 8 Non-Reproductive Decision-Making There are 2 outcomes to consider in this outcome domain.	**Limited importance**			**Important, but not critical**			**Critically important**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1. Results influences lifestyle changes Studies should report whether patients make any lifestyle changes based on RGCS results, such as weight loss, quitting smoking, or reducing alcohol intake.	❍	❍	❍	❍	❍	❍	❍	❍	❍
2. Results influenced decision-making regarding an insurance policy Studies should report whether patients make decisions about long-term care, disability, life insurance, or private health insurance (that covers IVF) based on RGCS results.	❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments
(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

Additional outcomes to suggest
(You can add suggestions for additional outcomes here or at the end of the survey)

Domain 9 Timeliness There are 4 outcomes to consider in this outcome domain.	**Limited importance**			**Important, but not critical**			**Critically important**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1. Turnaround times Studies should report the average and range (shortest and longest) turnaround time between sample collection and results return.	❍	❍	❍	❍	❍	❍	❍	❍	❍
2. Gestational age in the prenatal setting Studies should report the average and range (earliest and latest) gestational age at which specific tasks were completed, including gestational age when offered RGCS, gestational age when the sample was provided for RGCS, gestational age at the time of results, and gestational age when offered prenatal diagnosis (in increased risk couples), gestational age at the time of termination of pregnancy.	❍	❍	❍	❍	❍	❍	❍	❍	❍
3. Proportion of RGCS conducted with an ideal timeframe Studies should report the proportion of women that were screened preconception or by 12 weeks gestation.	❍	❍	❍	❍	❍	❍	❍	❍	❍
4. Time intervals between steps of the RGCS process Studies should report the time intervals between key steps of the RGCS process, including time between being offered RGCS and consenting to screening, time between consent and receiving results, time between maternal results and arranging partner testing (for sequential offers), and time between results and arrangement of follow-up genetic counselling with a specialist for increased risk couples, time between receipt of results and access to IVF/PGD.	❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments
(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

Additional outcomes to suggest
(You can add suggestions for additional outcomes here or at the end of the survey)

Domain 10 Patient attitudes, perceptions and beliefs related to RGCS There are 4 outcomes to consider in this outcome domain.	**Limited importance**			**Important, but not critical**			**Critically important**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1. Perceived chance of carrier finding and preparedness for an increased risk finding Studies should report patients perceived chance that they will have an increased risk finding on a scale from low to high, at the time of accepting screening.	❍	❍	❍	❍	❍	❍	❍	❍	❍
2. Patient attitude towards RGCS (at the time of the screening offer) Studies should report patients attitude regarding how they value the information that RGCS can provide on a scale from positive to negative, at the time of accepting screening.	❍	❍	❍	❍	❍	❍	❍	❍	❍
3. Patient attitude towards RGCS (after results) Studies should report patients attitude regarding the value of RGCS on a scale from positive to negative, after receiving results.	❍	❍	❍	❍	❍	❍	❍	❍	❍
4. Patient perception that RGCS will inform their reproductive decisions (at the time of the screening offer) Studies should report how patients perceive changing their reproductive plans if an increased risk result is returned.	❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments
(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

Additional outcomes to suggest
(You can add suggestions for additional outcomes here or at the end of the survey)

Domain 11 Deliberation and informed choice There are 5 outcomes to consider in this outcome domain.	**Limited importance**			**Important, but not critical**			**Critically important**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1. Patients spend time deliberating on the decision to accept or decline Studies should report patient perception that they had the opportunity to think about the screening offer before making a final decision to accept or decline the offer of RGCS.	❍	❍	❍	❍	❍	❍	❍	❍	❍
2. Patients had enough information to make an informed choice to accept or decline Studies should report patient perception that their information needs were met and they felt informed to make a decision to accept or decline the offer of RGCS.	❍	❍	❍	❍	❍	❍	❍	❍	❍
3. Patients were engaged in the decision-making process Studies should report patient perception that they were engaged in the discussion and decision-making to accept or decline the offer of RGCS.	❍	❍	❍	❍	❍	❍	❍	❍	❍
4. Patients made an informed choice to accept or decline testing Studies should report patient perception that they made an informed choice to accept or decline the offer of RGCS.	❍	❍	❍	❍	❍	❍	❍	❍	❍
5. Patients demonstrated that their knowledge, attitudes and decision to accept or decline RGCS were congruent Studies should report if patients made an informed choice as defined by the multi-dimensional measure of informed choice (MMIC). Example 1: a patient that has a good understanding of RGCS and the implications of an increased risk result, has a positive attitude that RGCS can provide valuable information, and accepts testing is considered to have made an informed choice. Example 2: If the patient has poor understanding or a negative attitude about RGCS but accepts testing anyway, they are not considered to have made an informed choice.	❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments

(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

Additional outcomes to suggest

(You can add suggestions for additional outcomes here or at the end of the survey)

Domain 12 Goals of pre- and post-test genetic counselling There are 7 outcomes to consider in this outcome domain.	**Limited importance**			**Important, but not critical**			**Critically important**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1. Genetic counselling presented screening and further testing as a choice Studies should report whether patients felt that they were offered voluntary choice to participate in RGCS, and if identified as increased risk during a pregnancy, that prenatal diagnosis was also offered as a choice.	❍	❍	❍	❍	❍	❍	❍	❍	❍
2. Genetic counselling provided sufficient information to meet patient needs Studies should report whether patients felt that they had all the information needed to make decisions.	❍	❍	❍	❍	❍	❍	❍	❍	❍
3. Timing and method of information provision promoted understanding Studies should report whether patients felt that the timing and method of information provided was adequate or could be improved to enhance understanding.	❍	❍	❍	❍	❍	❍	❍	❍	❍
4. Genetic counselling supported informed decision-making Studies should report whether patients felt that the healthcare provider helped them to deliberate and make an informed choice about RGCS and any further testing.	❍	❍	❍	❍	❍	❍	❍	❍	❍
5. Genetic counselling provider was knowledgeable and empathetic Studies should report whether patients felt that the healthcare provider was able to answer all their questions, and demonstrated an empathetic manner.	❍	❍	❍	❍	❍	❍	❍	❍	❍
6. Genetic counselling was accessible Studies should report whether patients felt that pre- and post-test genetic counselling was easily accessible.	❍	❍	❍	❍	❍	❍	❍	❍	❍

7. Genetic counselling promoted reproductive empowerment Studies should report whether patients felt that pre- and post-test genetic counselling facilitated an understanding of their reproductive choices and promoted a sense of confidence and empowerment to make choices that were aligned with their values.	❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments
(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

Additional outcomes to suggest
(You can add suggestions for additional outcomes here or at the end of the survey)

Domain 13 Knowledge and understanding There are 3 outcomes to consider in this outcome domain.	**Limited importance**			**Important, but not critical**			**Critically important**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1. Patient understanding of RGCS Studies should report patient knowledge which may include the role and significance of screening for those without existing family history or other prior increased risk, the range of conditions included in screening and possible results that can be returned, and options to consider if an increased risk result is received.	❍	❍	❍	❍	❍	❍	❍	❍	❍
2. Recall of screening result at a later timepoint Studies should report a patients ability to correctly recall their screening result at a future timepoint.	❍	❍	❍	❍	❍	❍	❍	❍	❍
3. Barriers and facilitators influencing patients understanding of RGCS Studies should report factors that influence patient understanding of RGCS, including aspects such as having access to a knowledgeable provider, methods of education prior to screening, and access to written/visual information.	❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments
(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

Additional outcomes to suggest
(You can add suggestions for additional outcomes here or at the end of the survey)

Domain 14 Acceptability of further testing and alternative reproductive options There are 3 outcomes to consider in this outcome domain.	**Limited importance**			**Important, but not critical**			**Critically important**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1. Patients personal preferences regarding prenatal diagnosis (PND), IVF with preimplantation genetic diagnosis (PGD), and termination of pregnancy (TOP) Studies should report patients personal values regarding PND, PGD and TOP.	❍	❍	❍	❍	❍	❍	❍	❍	❍
2. Patients religious views regarding prenatal diagnosis (PND), IVF with preimplantation genetic diagnosis (PGD), and termination of pregnancy (TOP) Studies should report patients religious views regarding PND, PGD and TOP.	❍	❍	❍	❍	❍	❍	❍	❍	❍
3. Patients perception of the societal acceptability of prenatal diagnosis (PND), IVF with preimplantation genetic diagnosis (PGD), and termination of pregnancy (TOP) Studies should report how the patient feels their decisions regarding PND, PGD and TOP are viewed by their wider social networks.	❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments
(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

Additional outcomes to suggest
(You can add suggestions for additional outcomes here or at the end of the survey)

Domain 15 Psychological wellbeing There are 7 outcomes to consider in this outcome domain.	**Limited importance**			**Important, but not critical**			**Critically important**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1. Impact of results to parental prenatal attachment Studies should report patients feelings of parental attachment to current pregnancy (in prenatal setting) or future pregnancies (in preconception setting).	❍	❍	❍	❍	❍	❍	❍	❍	❍
2. Anxiety Studies should report patient reported levels of anxiety.	❍	❍	❍	❍	❍	❍	❍	❍	❍
3. Grief and loss following an increased risk result Studies should report feelings of grief and loss related to increased risk results that impact a current pregnancy, and/or significantly alter the patients perception of their pregnancy journey in future pregnancies.	❍	❍	❍	❍	❍	❍	❍	❍	❍
4. Distress following an increased risk result Studies should report the impact of an increased risk result on the patient from the perspective of the impact of events scale (IES) which defines the result as a traumatic event that may have long lasting impacts on the psychological wellbeing of the patient.	❍	❍	❍	❍	❍	❍	❍	❍	❍
5. Uncertainty and resilience in patients following an increased risk result Studies should report the burden of uncertainty that patients feel following an increased risk result and their ability to cope with this uncertainty.	❍	❍	❍	❍	❍	❍	❍	❍	❍
6. Impact of results on patients perception of their own health Studies should report how the patients perception of their own health may change if identified as a carrier.	❍	❍	❍	❍	❍	❍	❍	❍	❍

7. Barriers and facilitators to patients psychological and emotional wellbeing during RGCS Studies should report factors directly related to RGCS that can be beneficial or detrimental to a patients emotional wellbeing, including aspects such as feeling informed and able to ask questions, or conversely feeling rushed or not given time for decisions.	❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments
(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

Additional outcomes to suggest
(You can add suggestions for additional outcomes here or at the end of the survey)

Domain 16 Decision satisfaction and regret There are 2 outcomes to consider in this outcome domain.	**Limited importance**			**Important, but not critical**			**Critically important**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1. Retrospective satisfaction with the decision to accept or decline RGCS Studies should report longitudinal (long-term) assessment of patients satisfaction or regret associated with their decision to accept or decline RGCS.	❍	❍	❍	❍	❍	❍	❍	❍	❍
2. Decisional regret associated with RGCS Studies should report longitudinal (long-term) assessment of patients satisfaction or regret associated with a decision that they made as a result of RGCS results, such as undertaking prenatal diagnosis, terminating a pregnancy, or accessing IVF.	❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments
(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

Additional outcomes to suggest
(You can add suggestions for additional outcomes here or at the end of the survey)

Domain 17 Privacy and stigmatisation concerns There are 3 outcomes to consider in this outcome domain.	**Limited importance**			**Important, but not critical**			**Critically important**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1. Patient concerns regarding stigmatisation Studies should report patients feelings of potential or actual stigmatisation based on RGCS results.	❍	❍	❍	❍	❍	❍	❍	❍	❍
2. Patient concerns regarding privacy and confidentiality Studies should report patients concern regarding the privacy and confidentiality of their RGCS results.	❍	❍	❍	❍	❍	❍	❍	❍	❍
3. Patient concerns regarding insurance Studies should report patients feelings of potential or actual discrimination by insurance companies based on RGCS results.	❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments
(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

Additional outcomes to suggest
(You can add suggestions for additional outcomes here or at the end of the survey)

Domain 18 Patient preferences There are 6 outcomes to consider in this outcome domain.	**Limited importance**			**Important, but not critical**			**Critically important**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1. Patient preference regarding which conditions are included in RGCS Studies should report patient preference for specific conditions to be included or excluded from RGCS.	❍	❍	❍	❍	❍	❍	❍	❍	❍
2. Patient preference regarding how many conditions are tested in RGCS Studies should report patient preference for small versus expanded panels.	❍	❍	❍	❍	❍	❍	❍	❍	❍
3. Patient preference regarding ethnicity-specific versus pan-ethnic screening Studies should report patient preference for only screening conditions that are indicated based on ethnic background, versus screening for a diverse and expanded panel of conditions regardless of ethnic background.	❍	❍	❍	❍	❍	❍	❍	❍	❍
4. Patient preference regarding the timing and setting of RGCS Studies should report patient preference for school-based, preconception, or prenatal offers of RGCS.	❍	❍	❍	❍	❍	❍	❍	❍	❍
5. Patient preference regarding the format of results Studies should report patient preference for receiving individual carrier findings versus couple-based increased findings.	❍	❍	❍	❍	❍	❍	❍	❍	❍
6. Patient preference regarding who offers RGCS Studies should report patient preference for healthcare providers that should offer RGCS, such as midwives, GPs, OBGYNs, or specialised genetic counselling services.	❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments

(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

Additional outcomes to suggest

(You can add suggestions for additional outcomes here or at the end of the survey)

Domain 19 Patient satisfaction with the processes of RGCS There are 3 outcomes to consider in this outcome domain.	**Limited importance**			**Important, but not critical**			**Critically important**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1. Satisfaction with accessibility, cost and convenience of the screening process Studies should report patients concerns regarding accessibility, cost and convenience of accessing RGCS.	❍	❍	❍	❍	❍	❍	❍	❍	❍
2. Satisfaction that information needs have been met Studies should report patient satisfaction with information and education that was provided during RGCS.	❍	❍	❍	❍	❍	❍	❍	❍	❍
3. Satisfaction with healthcare providers Studies should report patient satisfaction with the healthcare providers involved in their care when undertaking RGCS.	❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments
(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

Additional outcomes to suggest
(You can add suggestions for additional outcomes here or at the end of the survey)

Domain 20 Familial implications There are 4 outcomes to consider in this outcome domain.	**Limited importance**			**Important, but not critical**			**Critically important**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1. Dissemination of results to at-risk family members Studies should report the number of patients that communicated their results to at-risk family members.	❍	❍	❍	❍	❍	❍	❍	❍	❍
2. Impact of results on a couple's relationship Studies should report how patients perceive that RGCS has impacted their relationship with their reproductive partner, which may include strengthening or strain on the relationship.	❍	❍	❍	❍	❍	❍	❍	❍	❍
3. Impact of results on family relationship Studies should report how patients perceive that RGCS has impacted their relationship with family members, which may include strengthening or strain on the relationship.	❍	❍	❍	❍	❍	❍	❍	❍	❍
4. Support needs for dissemination of results to at-risk family members Studies should report the number of patients that requested assistance with communicating results to family members.	❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments
(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

Additional outcomes to suggest
(You can add suggestions for additional outcomes here or at the end of the survey)

Domain 21 Perceived utility of RGCS There are 3 outcomes to consider in this outcome domain.	**Limited importance**			**Important, but not critical**			**Critically important**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1. Reproductive empowerment Studies should report how empowered patients felt to make reproductive decisions that are right for them following RGCS.	❍	❍	❍	❍	❍	❍	❍	❍	❍
2. Birth rate of affected individuals Studies should report on the number of affected individuals born to patients that accessed RGCS.	❍	❍	❍	❍	❍	❍	❍	❍	❍
3. Timeliness of RGCS Studies should report the patient perception that RGCS was timed in a way that allowed them to consider their options and make informed decisions.	❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments
(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

Additional outcomes to suggest
(You can add suggestions for additional outcomes here or at the end of the survey)

Suggest new outcomes (optional)
You have reached the end of the outcome rankings. If you have any new outcomes to suggest that you feel were not represented previously, please indicate here and include a ranking of 1-9 for each outcome that you suggest. We will consider all new suggested outcomes for inclusion in the next round of the Delphi survey.

Consent to submit responses

In submitting my response, I am giving my consent to participate in the survey and I state that:

- I understand the purpose of the study, what I will be asked to do, and any risks/benefits involved.
- I have read the Participant Information Statement and have been able to discuss my involvement in the study with the researchers if I wished to do so.
- The researchers have answered any questions that I had about the study and I am happy with the answers.
- I understand that being in this study is completely voluntary and I do not have to take part. My decision whether to be in the study will not affect my relationship with the researchers or anyone else at the University of Technology Sydney now or in the future
- I understand that I can withdraw from the study at any time.
- I understand that my questionnaire responses cannot be withdrawn once they are submitted, as they will be grouped with other respondents and therefore the researchers will not be able to tell which one is mine.
- I understand that personal information about me that is collected over the course of this project will be stored securely and will only be used for purposes that I have agreed to.
- I understand that information about me will only be told to others with my permission, except as required by law.
- I understand that the results of this study may be published, and that publications will not contain my name or any identifiable information about me.

Supplementary material D.6: Outcomes excluded from Round 2

ID	Outcome description (n=36)
2.2	Identification of variants where the association with disease risk is unclear – studies should report the number of variants of uncertain significance identified through RGCS.
4.3	Decline of RGCS – studies should report the number of patients offered RGCS who decline the offer.
5.1	Uptake of pre-test genetic counselling – studies should report the number of patients that elect to discuss RGCS with their healthcare provider when offered.
5.2	Time required for pre-test genetic counselling – studies should report the length of time taken to explain and consent a patient for RGCS.
5.4	Mode of genetic counselling – studies should report the number of patients utilising face-to-face, telephone, or telehealth service.
8.1	Results influences lifestyle changes – studies should report whether patients make any lifestyle changes based on RGCS results, such as weight loss, quitting smoking, or reducing alcohol intake.
8.2	Results influenced decision-making regarding an insurance policy – studies should report whether patients make decisions about long-term care, disability, life insurance, or private health insurance (that covers IVF) based on RGCS results.
9.1	Turnaround times – studies should report the average and range (shortest and longest) turnaround time between sample collection and results return.
9.2	Gestational age in the prenatal setting – studies should report the average and range (earliest and latest) gestational age at which specific tasks were completed, including gestational age when offered RGCS, gestational age when the sample was provided for RGCS, gestational age at the time of results, and gestational age when offered prenatal diagnosis (in increased risk couples), gestational age at the time of termination of pregnancy.
9.3	Proportion of RGCS conducted with an ideal timeframe – studies should report the proportion of women that were screened preconception or by 12 weeks gestation.
9.4	Time intervals between steps of the RGCS process – studies should report the time intervals between key steps of the RGCS process, including time between being offered RGCS and consenting to screening, time between consent and receiving results, time between maternal results and arranging partner testing (for sequential offers), and time between results and arrangement of follow-up genetic counselling with a specialist for increased risk couples, time between receipt of results and access to IVF/PGD.
10.1	Perceived chance of carrier finding and preparedness for an increased risk finding – studies should report patients perceived chance that they will have an increased risk finding on a scale from low to high, at the time of accepting screening.
10.2	Patient attitude towards RGCS (at the time of the screening offer) – studies should report patients attitude regarding how they value the information that RGCS can provide on a scale from positive to negative, at the time of accepting screening.

10.3	Patient attitude towards RGCS (after results) – studies should report patients attitude regarding the value of RGCS on a scale from positive to negative, after receiving results.
11.1	Patients spend time deliberating on the decision to accept or decline – studies should report patient perception that they had the opportunity to think about the screening offer before making a final decision to accept or decline the offer of RGCS.
11.5	Patients demonstrated that their knowledge, attitudes and decision to accept or decline RGCS were congruent – studies should report if patients made an informed choice as defined by the multi-dimensional measure of informed choice (MMIC). Example 1: a patient that has a good understanding of RGCS and the implications of an increased risk result, has a positive attitude that RGCS can provide valuable information, and accepts testing is considered to have made an informed choice. Example 2: If the patient has poor understanding or a negative attitude about RGCS but accepts testing anyway, they are not considered to have made an informed choice.
12.3	Timing and method of information provision promoted understanding – studies should report whether patients felt that the timing and method of information provided was adequate or could be improved to enhance understanding.
12.5	Genetic counselling provider was knowledgeable and empathetic – studies should report whether patients felt that the healthcare provider was able to answer all their questions, and demonstrated an empathetic manner.
14.1	Patients personal preferences regarding prenatal diagnosis (PND), IVF with preimplantation genetic diagnosis (PGD), and termination of pregnancy (TOP) – studies should report patients personal values regarding PND, PGD and TOP.
14.2	Patients religious views regarding prenatal diagnosis (PND), IVF with preimplantation genetic diagnosis (PGD), and termination of pregnancy (TOP) – studies should report patients religious views regarding PND, PGD and TOP.
14.3	Patients perception of the societal acceptability of prenatal diagnosis (PND), IVF with preimplantation genetic diagnosis (PGD), and termination of pregnancy (TOP) – studies should report how the patient feels their decisions regarding PND, PGD and TOP are viewed by their wider social networks.
15.1	Impact of results to parental prenatal attachment – studies should report patients feelings of parental attachment to current pregnancy (in prenatal setting) or future pregnancies (in preconception setting).
17.1	Patient concerns regarding stigmatisation – studies should report patients feelings of potential or actual stigmatisation based on RGCS results.
17.2	Patient concerns regarding privacy and confidentiality – studies should report patients concern regarding the privacy and confidentiality of their RGCS results.
17.3	Patient concerns regarding insurance – studies should report patients feelings of potential or actual discrimination by insurance companies based on RGCS results.
18.1	Patient preference regarding which conditions are included in RGCS – studies should report patient preference for specific conditions to be included or excluded from RGCS.
18.2	Patient preference regarding how many conditions are tested in RGCS – studies should report patient preference for small versus expanded panels.
18.3	Patient preference regarding ethnicity-specific versus pan-ethnic screening – studies should report patient preference for only screening conditions that are

	indicated based on ethnic background, versus screening for a diverse and expanded panel of conditions regardless of ethnic background.
18.4	Patient preference regarding the timing and setting of RGCS – studies should report patient preference for school-based, preconception, or prenatal offers of RGCS.
18.5	Patient preference regarding the format of results – studies should report patient preference for receiving individual carrier findings versus couple-based increased findings.
18.6	Patient preference regarding who offers RGCS – studies should report patient preference for healthcare providers that should offer RGCS, such as midwives, GPs, OBGYNs, or specialised genetic counselling services.
19.3	Satisfaction with healthcare providers – studies should report patient satisfaction with the healthcare providers involved in their care when undertaking RGCS.
20.1	Dissemination of results to at-risk family members – studies should report the number of patients that communicated their results to at-risk family members.
20.3	Impact of results on family relationship – studies should report how patients perceive that RGCS has impacted their relationship with family members, which may include strengthening or strain on the relationship.
20.4	Support needs for dissemination of results to at-risk family members – studies should report the number of patients that requested assistance with communicating results to family members.
21.3	Timeliness of RGCS – studies should report the patient perception that RGCS was timed in a way that allowed them to consider their options and make informed decisions.

Supplementary material D.7: Outcome eligible for inclusion in Round 2

ID	Outcome description (n=46)
1.1	Carrier detection rate - studies should report the number of heterozygous carriers identified.
1.2	Identification of increased risk couples - studies should report the number of increased risk couples identified (defined as both members of a reproductive couple being carriers of the same recessive condition, or the female member being a carrier of an X-linked condition).
2.1	Identification of results which indicate the prospective parent undertaking RGCS is at increased risk or affected with one of the conditions screened - studies should report the number of homozygous, hemizygous or compound heterozygous individuals identified through RGCS.
3.1	Laboratory errors leading to the incorrect interpretation of results - studies should report the rate of laboratory errors (such as sample mix-ups or contamination of samples) that lead to the reporting of incorrect results. This includes false negatives (where the patient receives a negative result indicating they are NOT a carrier, however is later found to be a carrier), and false positives (where the patient receives a positive result indicating they are a carrier, however this is later found to be incorrect).
3.2	Test failure and requests for replacement samples - studies should report the rate of test failure as a result of insufficient or poor-quality DNA.
4.1	Number of RGCS tests - studies should report the number of screening tests conducted.
4.2	Uptake of RGCS - studies should report the number of patients offered RGCS that accept the offer and consent to screening.
4.4	Barriers and facilitators to access and uptake of RGCS
5.3	Uptake of post-test genetic counselling for increased risk couples - for studies where RGCS is offered by a non-genetics health professional (GP, midwife or maternal fetal specialist), studies should report the number of increased risk couples that accepted an offer of post-test counselling with a genetic health professional (genetic counsellor or clinical geneticist).
6.1	Uptake of partner testing (in sequential screening) - sequential screening refers to studies where RGCS is offered to one reproductive partner first, and then partner testing offered if a carrier finding is returned. Studies should report the number of patients who elect to test their reproductive partner when they are found to be a carrier of a recessive condition.
6.2	Barriers and facilitators to access and uptake of partner testing - studies should report the factors involved in decision-making to test a reproductive partner, including aspects such as cost and convenience of the process.
6.3	Uptake of prenatal diagnosis - studies should report the number of patients that accept and decline prenatal diagnosis (CVS or amniocentesis) to determine the genetic status of an at-risk pregnancy following an increased risk result from RGCS.
6.4	Barriers and facilitators to access and uptake of prenatal diagnosis - studies should report the factors involved in decision-making to have a CVS or amniocentesis following an increased risk RGCS results, including aspects such as risks associated with invasive procedures, and that they wouldn't terminate a pregnancy based on result based on cultural, moral, religious beliefs or the condition being treatable.

6.6	Barriers and facilitators of patient uptake of IVF/PGD in increased risk couples – studies should report factors that influence uptake of IVF/PGD, including aspects such as access, cost, medicalisation of the pregnancy journey, and whether the patients are already having IVF or fertility issues.
6.7	Barriers and facilitators of patients experience of PND, IVF/PGD and TOP – studies should report external factors such as the healthcare and social context that may impact patients undergoing PND, IVF/PGD and TOP, including aspects such as access to services and financial considerations.
6.8	Support needs when making reproductive decisions – studies should report the number of patients that requested sources of additional information, such as support groups or connection with those with lived experience of a genetic condition, to inform their reproductive decisions.
7.1	Results of prenatal diagnosis (CVS or amniocentesis) – studies should report the number of affected pregnancies identified through prenatal diagnosis.
7.2	Rate of fetal loss following prenatal diagnosis (CVS or amniocentesis) – studies should report the number of pregnancies that miscarried following prenatal diagnosis.
7.3	Decision to continue or terminate a pregnancy identified to be affected through prenatal diagnosis – studies should report the number of affected pregnancies that were terminated following results of prenatal diagnosis.
7.4	Birth rates for conditions that were included in screening – studies should report the number of babies born affected with a condition that was screened for. This may be because parents chose to proceed with a pregnancy known to be affected, may have been aware of increased risk but chose not to test during the pregnancy, or because of a laboratory error that missed identifying an increased risk.
7.5	Results of IVF with preimplantation diagnosis (PGD) utilised by increased risk couples in subsequent pregnancies – studies should report the number of unaffected ongoing pregnancies following IVF with PGD.
10.4	Patient perception that RGCS will inform their reproductive decisions (at the time of the screening offer) – studies should report how patients perceive changing their reproductive plans if an increased risk result is returned.
11.2	Patients had enough information to make an informed choice to accept or decline – studies should report patient perception that their information needs were met and they felt informed to make a decision to accept or decline the offer of RGCS.
11.3	Patients were engaged in the decision-making process – studies should report patient perception that they were engaged in the discussion and decision-making to accept or decline the offer of RGCS.
11.4	Patients made an informed choice to accept or decline testing – studies should report patient perception that they made an informed choice to accept or decline the offer of RGCS.
12.1	Genetic counselling presented screening and further testing as a choice – studies should report whether patients felt that they were offered voluntary choice to participate in RGCS, and if identified as increased risk during a pregnancy, that prenatal diagnosis was also offered as a choice.
12.2	Genetic counselling provided sufficient information to meet patient needs – studies should report whether patients felt that they had all the information needed to make decisions.

12.4	Genetic counselling supported informed decision-making - studies should report whether patients felt that the healthcare provider helped them to deliberate and make an informed choice about RGCS and any further testing.
12.6	Genetic counselling was accessible - studies should report whether patients felt that pre- and post-test genetic counselling was easily accessible.
12.7	Genetic counselling promoted reproductive empowerment - studies should report whether patients felt that pre- and post-test genetic counselling facilitated an understanding of their reproductive choices and promoted a sense of confidence and empowerment to make choices that were aligned with their values.
13.1	Patient understanding of RGCS - studies should report patient knowledge which may include the role and significance of screening for those without existing family history or other prior increased risk, the range of conditions included in screening and possible results that can be returned, and options to consider if an increased risk result is received.
13.2	Recall of screening result at a later timepoint - studies should report a patients ability to correctly recall their screening result at a future timepoint.
13.3	Barriers and facilitators influencing patients understanding of RGCS - studies should report factors that influence patient understanding of RGCS, including aspects such as having access to a knowledgeable provider, methods of education prior to screening, and access to written/visual information.
15.2	Anxiety - studies should report patient reported levels of anxiety.
15.3	Grief and loss following an increased risk result - studies should report feelings of grief and loss related to increased risk results that impact a current pregnancy, and/or significantly alter the patients perception of their pregnancy journey in future pregnancies.
15.4	Distress following an increased risk result - studies should report the impact of an increased risk result on the patient from the perspective of the impact of events scale (IES) which defines the result as a traumatic event that may have long lasting impacts on the psychological wellbeing of the patient.
15.5	Uncertainty and resilience in patients following an increased risk result - studies should report the burden of uncertainty that patients feel following an increased risk result and their ability to cope with this uncertainty.
15.6	Impact of results on patients perception of their own health - studies should report how the patients perception of their own health may change if identified as a carrier.
15.7	Barriers and facilitators to patients psychological and emotional wellbeing during RGCS - studies should report factors directly related to RGCS that can be beneficial or detrimental to a patients emotional wellbeing, including aspects such as feeling informed and able to ask questions, or conversely feeling rushed or not given time for decisions.
16.1	Retrospective satisfaction with the decision to accept or decline RGCS - studies should report longitudinal (long-term) assessment of patients satisfaction or regret associated with their decision to accept or decline RGCS.
16.2	Decisional regret associated with RGCS - studies should report longitudinal (long-term) assessment of patients satisfaction or regret associated with a decision that they made as a result of RGCS results, such as undertaking prenatal diagnosis, terminating a pregnancy, or accessing IVF.

19.1	Satisfaction with accessibility, cost and convenience of the screening process – studies should report patients concerns regarding accessibility, cost and convenience of accessing RGCS.
19.2	Satisfaction that information needs have been met – studies should report patient satisfaction with information and education that was provided during RGCS.
20.2	Impact of results on a couple's relationship – studies should report how patients perceive that RGCS has impacted their relationship with their reproductive partner, which may include strengthening or strain on the relationship.
21.1	Reproductive empowerment – studies should report how empowered patients felt to make reproductive decisions that are right for them following RGCS.
21.2	Birth rate of affected individuals – studies should report on the number of affected individuals born to patients that accessed RGCS.

Supplementary material D.8: Outcomes combined for Round 2

ID	Outcome description
1.1 and 1.2	**Carrier and couple detection rates** - studies should report the number of heterozygous carriers identified and/or the number of increased risk couples identified as appropriate for the study design
2.1 and 2.2	**Identification of secondary or incidental findings** - studies should report any results that were secondary to the primary carrier screening results, including the number of variants of uncertain significance if reported back to patients, or the number of homozygous, hemizygous or compound heterozygous findings that indicate that a healthy prospective parent undertaking RGCS is at risk or affected with one of the screened conditions
3.1 and 3.2	**Technical laboratory outcomes** - studies should report any technical laboratory outcomes that impact on the patient experience of RGCS and/or on the interpretation of results. This includes: laboratory errors that lead to the incorrect interpretation of results, such as sampling or contamination errors, false negatives, or false positives; the rate of test failure as a result of insufficient or poor-quality DNA
4.1 and 4.2	**Uptake of RGCS** - studies should report an appropriate outcome to capture uptake within the scope of their study design. This includes: The number of patients offered RGCS; the number of patients that accept; where the two previous outcomes are not available, the number of screening tests conducted may be used as a proxy for uptake.
6.2, 6.4, 6.6 and 6.7	**Barriers and facilitators related to uptake of further testing and reproductive decision-making** - studies should report the factors influencing reproductive decisions relevant to their study. This includes: Uptake of partner testing (for studies with a sequential study design where one reproductive partner is screened first, followed by the other partner only if there is a carrier finding reported) Uptake of prenatal diagnosis (CVS or amniocentesis) Uptake of IVF with pre-implantation genetic diagnosis
11.2, 11.3, and 11.4	**Informed choice** - studies should assess whether patients made an informed choice to accept or decline screening

12.1, 12.2, 12.4, 12.5, and 12.7	**Goals of pre- and post-test genetic counselling** – studies should report whether patients felt that pre- and post-test genetic counselling met their needs and expectations, including aspects such as being presented with a choice to accept or decline, whether they felt enough information was provided to make choices, whether the manner of the healthcare provider was empathetic and appropriate, whether the healthcare provider was accessible, and whether the healthcare provider facilitated an understanding of reproductive choices and encouraged a sense of confidence and empowerment
16.1 and 16.2	**Decisional satisfaction or regret related to RGCS** – studies should report longitudinal (long-term) assessment of patients satisfaction or regret associated with their decision to accept or decline RGCS, and associated with decisions they made based on RGCS results such as undertaking prenatal diagnosis, terminating an affected pregnancy, or accessing IVF
1.1 and 1.2	**Carrier and couple detection rates** - studies should report the number of heterozygous carriers identified and/or the number of increased risk couples identified as appropriate for the study design

Supplementary material D.9: Guidance for participants document – Round 2

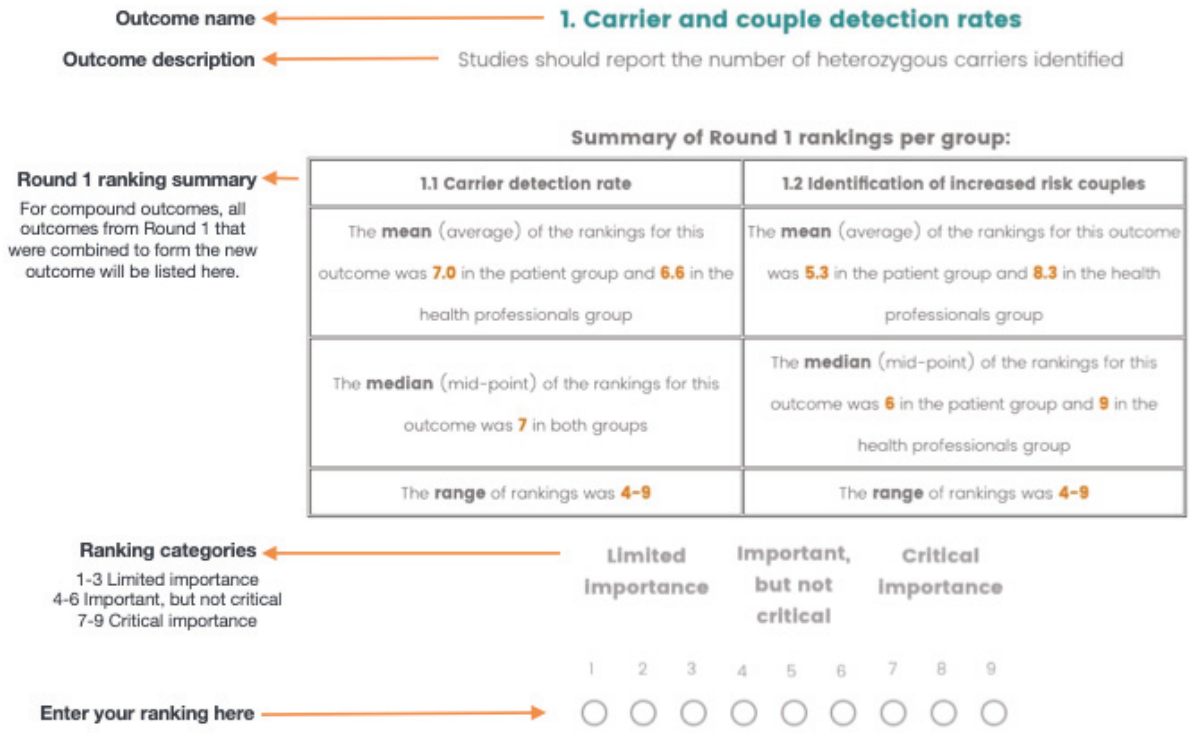
How do I answer the questions?

You have been assigned a study ID between 1 and 12. This ID can be found in the email that you were sent that contained the link to this survey. As you proceed through Round 2, use your study ID to remind yourself of the ranking that you gave each item in Round 1. For example, in the table below if your assigned study ID is 6, you can see that you previously ranked this outcome as an 8 (on the scale from 1 to 9).

Study ID (find your study ID in the email in which you accessed the link to this survey)	**Round 1 Rankings** **1-3** (limited importance) **4-6** (important, but not critical) **7-9** (critical importance)
1	5
2	6
3	7
4	8
5	4
6	8
7	9
8	8
9	8
10	5
11	6
12	6

You can compare your Round 1 ranking to other participants and review the summary of the outcome to decide if you would like to change your ranking of this outcome. As in the example below, you will see the mean, median and range of Round 1 rankings. These are split into two groups to show the difference, if any, between the rankings provided by patients and health professionals participating in this Delphi survey. You are not obligated to change your ranking if you are happy with your initial ranking.

When you have decided whether to keep your original ranking, or to change it, indicate your choice on the 1-9 scale. Below is a guidance diagram to breakdown the question format in Round 2.



When re-ranking each outcome, decide whether you believe this outcome:

- should be measured and reported in **ALL** future studies on RGCS. If so select a score between 7 and 9; or
- does not need to be measured and reported in all future studies, but could be important for some future research to focus on. If so, select a score between 4 and 6
- has limited importance and probably doesn't need to be included in research. If so, select a score between 1 and 3

If you have any questions that are not addressed here, do not hesitate to contact me at **ebony.richardson@uts.edu.au**

Supplementary material D.10: Round 2 Delphi survey

Introduction to CODECS Study Delphi Survey - Round 2

Thank you for your participation in the first round of the Core Outcome Development for Carrier Screening (CODECS) Delphi Survey. You are now about to undertake Round 2. Before you begin, the results of Round 1 have been summarised below. **You should read through this summary before proceeding.**

Based on your rankings in Round 1, we have significantly reduced the list of 83 outcomes from previous studies of reproductive genetic carrier screening (RGCS) that we are considering for inclusion in a core outcome set.

One outcome reached consensus as being critically important to include in all future studies of RGCS after Round 1:

Reproductive decisions following an increased risk result
Studies should report the reproductive decisions made by patients based on RGCS, including the decision to continue or terminate a pregnancy determined to be affected through prenatal diagnosis, uptake of IVF with PGD in future pregnancies, decision to proceed with natural conception and test future pregnancies, the decision to not have children or have a smaller family than initially planned, or use of an egg or sperm donor.

This outcome has been included in our preliminary core outcome set and does not need to be re-ranked in Round 2.

33 outcomes reached consensus that they were not critically important to include in a core outcome set, and these have been excluded from Round 2.

49 outcomes did not reach consensus after Round 1. Some of these outcomes have been re-worded or combined based on your comments and feedback in Round 1. As such, there are **32** outcomes to re-rank in Round 2.

No new outcomes were suggested by participants in Round 1.

A few clarifications:

Participant feedback highlighted that certain outcomes may be dependent on the study design or way in which RGCS is being offered. We have added a caveat where appropriate to reflect this. Please rank these outcomes according to their importance in studies of their specific type.

Participant feedback also highlighted that some outcomes were interesting or 'nice to have' but might not need to be included in all studies, or might not be feasible to do so. You can rank these in the 4-6 category, which indicates that outcomes are important but not critical.

What is involved in Round 2?

You will be ranking outcomes in the same way that you did in Round 1, with the additional

benefit of being able to see the results of Round 1 to inform how you re-rank the outcome. More detailed instructions are provided on the next page.

For this second round of rankings we ask you to focus on which of these outcomes you think are **critical** for inclusion in a core outcome set, meaning that they will be recommended for **ALL** future studies to measure and report. A list of the included outcomes that you will be re-ranking has been provided, you should download **this pdf** now and scan over the full list of outcomes to get an initial idea of which outcomes you might want to prioritise. Tick boxes have been provided if you would like to use these to track the outcomes you want to rank as 7-9 (critically important). You will re-rank each of these outcomes individually as you progress through the survey.

Key definitions and answers to common questions to assist you in completing this survey can be found **here**.

This survey will be open for 4 weeks.

This study has received Ethics approval from The University of Technology Sydney Ethics Committee (UTS HREC ETH20-5179). For more information please read the **Participant information sheet**.

By clicking on the 'Next' button below, you are indicating that you understand that the data that you provide in this survey will be collected and retained by researchers from the University of Technology Sydney. If you do not wish to continue to the Delphi survey, please close your browser window to exit the survey.

End of Block: Patient Information and Round 1 Summary

Start of Block: Instructions for Round 2

Instructions for ranking outcomes in Round 2:

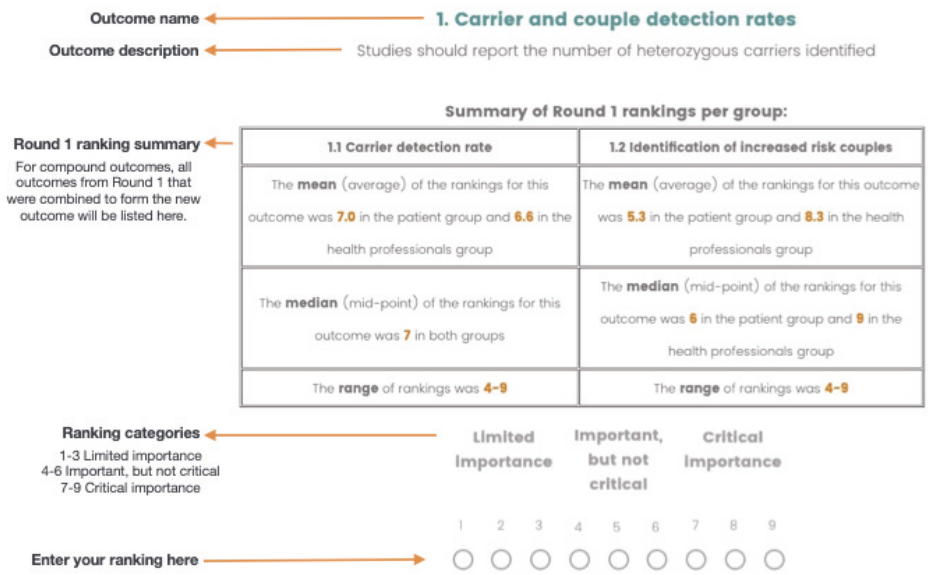
Please read these instructions carefully as they will ensure that you have all the information needed to complete the survey.

You have been assigned a study ID between 1 and 12. This ID can be found in the email that contained the link to this survey. As you proceed through Round 2, use your study ID to remind yourself of the ranking that you gave each item in Round 1. For example, in the table below if your assigned study ID is 6, you can see that you previously ranked this outcome as an 8 (on the scale from 1 to 9).

Study ID	1. Example outcome ranking
1	5
2	6
3	7
4	8
5	4
6	8
7	9
8	8
9	8
10	5
11	6
12	6

You can compare your Round 1 ranking to other participants and review the summary of the outcome to decide if you would like to change your ranking of this outcome in Round 2. As in the example below, you will see the mean, median and range of Round 1 rankings. These are split into two groups to show the difference, if any, between the rankings provided by patients and health professionals participating in this Delphi survey. You are not obligated to change your ranking if you are happy with your initial ranking.

When you have decided whether to keep your original ranking, or to change it, indicate your choice on the 1-9 scale. Below is a guidance diagram to breakdown the question format in Round 2.



If you would like to provide a comment or clarify the reason behind your rating, please do so in the box provided. Providing a reason or comment in the box is optional and does not need to be completed for each question.

Please enter a rating for all outcomes. There are no right or wrong responses. We are interested in your opinion.

Your participation is voluntary. You may exit the survey at any time and your progress will be saved. You can return to complete the survey at a later time by using the same personalised link. You can see your progress through the survey indicated by the progress bar at the top of your screen. By clicking submit at the end of the survey you are consenting for your data to be used for research purposes. Please contact ebony.richardson@uts.edu.au if you encounter any issues or require assistance with completing the survey.

When you are ready to begin reviewing the outcomes in Round 2 select "proceed to rankings".

End of Block: Instructions for Round 2

Start of Block: Domain 1 - Primary laboratory outcomes

Outcome Domain 1 of 16: Primary Laboratory Outcomes

Results from Round 1

There were **2** outcomes in this domain in Round 1. Participants noted that these outcomes would depend on whether RGCS was offered sequentially (where individual carrier results are reported for each reproductive partner) or couple-based (where only reproductive risk as a couple is reported). Following this feedback, we have merged these two outcomes:

Carrier and couple detection rates

Studies should report the number of heterozygous carriers identified and/or the number of increased risk couples identified as appropriate for the study design.

There are three steps to re-ranking each outcome:

- Use your study ID (in the table below) to check what your rankings were in Round 1
- Review the summary scores (mean, median and range) to understand how other participants ranked the outcome
- Decide whether you believe the outcome:
    - Should be measured and reported in **ALL** future studies on RGCS. If so, select a score between 7 and 9
    - Does not need to be measured and reported in all future studies, but could be important for some future research to focus on. If so, select a score between 4 and 6
    - Has limited importance and probably doesn't need to be included in any future research. If so, select a score between 1 and 3.

Section 1: Round 1 Rankings

Study ID	1.1 Carrier detection rate	1.2 Identification of increased risk couples
1	5	9
2	6	9
3	7	8
4	8	9
5	4	6
6	8	9
7	9	4
8	8	6
9	8	5
10	5	5
11	6	6
12	6	6
	Outcomes 1.1 and 1.2 have been merged in Round 2	

Section 2: Outcomes for Round 2

1. Carrier and couple detection rates

Studies should report the number of heterozygous carriers identified and/or the number of increased risk couples identified as appropriate for the study design.

Summary of Round 1 rankings per group:

1.1 Carrier detection rate	1.2 Identification of increased risk couples
The **mean** (average) of the rankings for this outcome was **7.0** in the patient group and **6.6** in the health professionals group	The **mean** (average) of the rankings for this outcome was **5.3** in the patient group and **8.3** in the health professionals group
The **median** (mid-point) of the rankings for this outcome was **7** in both groups	The **median** (mid-point) of the rankings for this outcome was **6** in the patient group and **9** in the health professionals group
The **range** of rankings was **4-9**	The **range** of rankings was **4-9**

Limited importance			Important, but not critical			Critically important		
1	2	3	4	5	6	7	8	9
❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments

(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

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_____

End of Block: Domain 1 - Primary laboratory outcomes

Start of Block: Domain 2 - Secondary and incidental laboratory outcomes

Outcome Domain 2 of 16: Secondary or Incidental Laboratory Outcomes

Results from Round 1

There were **2** outcomes in this domain in Round 1. Feedback suggested that these outcomes could be important depending on the study design. In regards to variants of uncertain significance (VUS), a number of participants expressed the view that these are not appropriate to report in RGCS at a population level. Pease consider whether this is an important outcome to report if the lab does include VUS in their screening. Following the feedback on these outcomes, we have merged them into a new outcome:

Identification of secondary or incidental findings

Studies should report any results that were secondary or incidental to the primary carrier screening results, including the number of variants of uncertain significance if reported back to patients, or the number of homozygous, hemizygous or compound heterozygous findings that indicate that a healthy prospective parent undertaking RGCS is at risk or affected with one of the screened conditions.

Section 1: Round 1 Rankings

Study ID	2.1 Identification of results which indicate the prospective parent undertaking RGCS is at increased risk or affected with one of the conditions screened	2.2 Identification of variants where the association with disease risk is unclear
1	5	4
2	9	1
3	8	6
4	6	1
5	7	2
6	8	5
7	4	7
8	8	7
9	8	7
10	5	5
11	7	7
12	9	5
	Outcomes 2.1 and 2.2 have been merged in Round 2	

Section 2: Outcomes for Round 2

1. Identification of secondary or incidental findings

Studies should report any results that were secondary to the primary carrier screening results, including the number of variants of uncertain significance if reported back to patients, or the number of homozygous, hemizygous or compound heterozygous findings that indicate that a healthy prospective parent undertaking RGCS is at risk or affected with one of the screened conditions.

Summary of Round 1 rankings per group:

2.1 Identification of results which indicate the prospective parent undertaking RGCS is at increased risk or affected with one of the conditions screened	**2.2 Identification of variants where the association with disease risk is unclear**
The **mean** (average) of the rankings for this outcome was **6.8** in the patient group and **7.2** in the health professionals group	The **mean** (average) of the rankings for this outcome was **6.3** in the patient group and **3.2** in the health professionals group
The **median** (mid-point) of the rankings for this outcome was **8** in both groups	The **median** (mid-point) of the rankings for this outcome was **7** in the patient group and **3** in the health professionals group
The **range** of rankings was **4-9**	The **range** of rankings was **1-7**

Limited importance			**Important, but not critical**			**Critically important**		
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments

(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

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End of Block: Domain 2 - Secondary and incidental laboratory outcomes

Start of Block: Domain 3 - Technical laboratory outcomes

Outcome Domain 3 of 16: Technical Laboratory Outcomes

Results from Round 1

There were **2** outcomes in this domain in Round 1. Feedback suggested that these outcomes were viewed as likely to be rare when RGCS is conducted through appropriately accredited laboratories, however even if the incidence would be low these may be important outcomes to evaluate the quality of screening laboratories. Following your feedback we have merged these two outcomes into one:

Technical laboratory outcomes

Studies should report any technical laboratory outcomes that impact on the patient experience of RGCS and/or on the interpretation of results. This includes: laboratory errors that lead to the incorrect interpretation of results, such as sampling or contamination errors, false negatives, or false positives; the rate of test failure as a result of insufficient or poor-quality DNA.

Section 1: Round 1 Rankings

Study ID	3.1 Laboratory errors leading to the incorrect interpretation of results	3.2 Test failure and requests for replacement samples
1	6	7
2	6	5
3	8	9
4	4	6
5	7	7
6	4	4
7	8	5
8	8	5
9	8	8
10	8	8
11	8	8
12	6	6
	Outcomes 3.1 and 3.2 have been merged in Round 2	

Section 2: Outcomes for Round 2

1. Technical laboratory outcomes

Studies should report any technical laboratory outcomes that impact on the patient experience of RGCS and/or on the interpretation of results. This includes: laboratory errors that lead to the incorrect interpretation of results, such as sampling or contamination errors, false negatives, or false positives; the rate of test failure as a result of insufficient or poor-quality DNA.

Summary of Round 1 rankings per group:

3.1 Laboratory errors leading to the incorrect interpretation of results	3.2 Test failure and requests for replacement samples
The **mean** (average) of the rankings for this outcome was **7.7** in the patient group and **5.8** in the health professionals group	The **mean** (average) of the rankings for this outcome was **6.7** in the patient group and **6.3** in the health professionals group
The **median** (mid-point) of the rankings for this outcome was **8** in both groups	The **median** (mid-point) of the rankings for this outcome was **7** in both groups
The **range** of rankings was **4-8**	The **range** of rankings was **4-9**

Limited importance			Important, but not critical			Critically important		
1	2	3	4	5	6	7	8	9
❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments

(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

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_____

End of Block: Domain 3 - Technical laboratory outcomes

Start of Block: Domain 4 - Uptake of services

Outcome Domain 4 of 16: Uptake of services

Results from Round 1

There were **4** outcomes in this domain in Round 1, one of which has been excluded based on Round 1 rankings. Feedback suggested that uptake was valued as an important outcome in this setting. Participants did not think decliners of RGCS was a necessary outcome, and can be inferred if you have the base number of how many patients were offered screening and the number who accepted. Many comments also highlighted that there may be practical difficulties in how uptake can be captured based on study design. Following this feedback we merged relevant outcomes into a new outcome:

Uptake of RGCS

Studies should report an appropriate outcome to capture uptake within the scope of their study design. This includes:

- *The number of patients offered RGCS;*
- *The number of patients that accept;*
- *Where the two previous outcomes are not available, the number of screening tests conducted may be used as a proxy for uptake.*

No changes were made to the fourth outcome in this domain.

Section 1: Round 1 Rankings

Study ID	4.1 Number of RGCS tests	4.2 Uptake of RGCS	4.4 Barriers and facilitators to access and uptake
1	8	5	3
2	6	4	7
3	8	8	5
4	9	6	3
5	7	8	6
6	7	8	8
7	8	4	2
8	5	3	3
9	9	9	7
10	4	5	1
11	8	8	6
12	8	8	5
	These outcomes have been merged for Round 2		No changes were made to this outcome

Section 2: Outcomes for Round 2

1. Uptake of RGCS

Studies should report an appropriate outcome to capture uptake within the scope of their study design. This includes:

- The number of patients offered RGCS;
- The number of patients that accept;

- Where the two previous outcomes are not available, the number of screening tests conducted may be used as a proxy for uptake.

Summary of Round 1 rankings per group:

4.1 Number of RGCS tests	4.2 Uptake of RGCS
The **mean** (average) of the rankings for this outcome was **7.0** in the patient group and **7.5** in the health professionals group	The **mean** (average) of the rankings for this outcome was **6.2** in the patient group and **6.5** in the health professionals group
The **median** (mid-point) of the rankings for this outcome was **8** in both groups	The **median** (mid-point) of the rankings for this outcome was **7** in both groups
The **range** of rankings was **4-9**	The **range** of rankings was **3-9**

Limited importance			Important, but not critical			Critically important		
1	2	3	4	5	6	7	8	9
❍	❍	❍	❍	❍	❍	❍	❍	❍

2. Barriers and facilitators to access and uptake

Studies should report patient perception of the accessibility of RGCS and how this influences their decision to have it. Accessibility includes aspects such as cost and convenience of the process.

Summary of Round 1 rankings per group:

4.4 Barriers and facilitators to access and uptake
The **mean** (average) of the rankings for this outcome was **6.5** in the patient group and **6.8** in the health professionals group
The **median** (mid-point) of the rankings for this outcome was **8** in both groups
The **range** of rankings was **2-9**

Limited importance			Important, but not critical			Critically important		
1	2	3	4	5	6	7	8	9
❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments

(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

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End of Block: Domain 4 - Uptake of services

Start of Block: Domain 5 - Genetic counselling resource use

Outcome Domain 5 of 16: Genetic counselling resource use

Results from Round 1

There were **4** outcomes in this domain in Round 1, three of which have been excluded based on Round 1 rankings. The remaining outcome was noted by participants to be dependent on study design. For this outcome, consider whether you think this is a critical outcome to report in all studies where RGCS is offered by a non-genetics health professional, including GPs, midwives, OBGYN and maternal fetal specialists.

Section 1: Round 1 Rankings

Study ID	5.1 Uptake of post-test genetic counselling for increased risk couples
1	7
2	9
3	8
4	7
5	9
6	8
7	4
8	3
9	7
10	5
11	7
12	7
	No changes were made to this outcome

Section 2: Outcomes for Round 2

1. Uptake of post-test genetic counselling for increased risk couples

For studies where RGCS is offered by a non-genetics health professional (GP, midwife or OBGYN/maternal fetal specialist), studies should report the number of increased risk couples that accepted an offer of post-test counselling with a genetic health professional (genetic counsellor or clinical geneticist).

Summary of Round 1 rankings per group:

5.1 Uptake of post-test genetic counselling for increased risk couples
The **mean** (average) of the rankings for this outcome was **5.5** in the patient group and **8.0** in the health professionals group
The **median** (mid-point) of the rankings for this outcome was **6** in the patient group and **8** in the health professionals group
The **range** of rankings was **3-9**

Limited importance			Important, but not critical			Critically important		
1	2	3	4	5	6	7	8	9
❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments

(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

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_____

End of Block: Domain 5 - Genetic counselling resource use

Start of Block: Domain 6 - Further testing and reproductive decision-making

Outcome Domain 6 of 16: Further testing and reproductive decision-making

Results from Round 1

There were **8** outcomes in this domain in Round 1. One of these reached consensus as being critically important and does not need to be re-ranked in this round. Scoring was similar between 4 proposed outcomes related to barriers and facilitators in this domain. As such, we have merged these into one new outcome:

Barriers and facilitators related to further testing and reproductive decision-making

Studies should report the factors influencing reproductive decisions relevant to their study. This includes:

- *Uptake of partner testing (for studies with a sequential study design where one reproductive partner is screened first, followed by the other partner only if there is a carrier finding reported)*
- *Uptake of prenatal diagnosis (CVS or amniocentesis)*
- *Uptake of IVF with pre-implantation genetic diagnosis.*

Section 1: Round 1 Rankings

Study ID	6.1 Uptake of partner screening	6.3 Uptake of prenatal diagnosis	6.2 Barriers and facilitators to access and uptake of partner screening	6.4 Barriers and facilitators to access and uptake of prenatal diagnosis	6.5 Barriers and facilitators to access and uptake of IVF/PGD	6. Barriers and facilitators to patient experience of IVF/PGD	6.7 Support needs when making reproductive decisions
1	7	7	3	3	3	3	4
2	8	9	8	9	9	9	7
3	5	6	8	6	6	6	9
4	9	9	9	9	9	9	7
5	8	9	8	9	9	9	9
6	7	9	8	9	9	9	9
7	7	5	9	8	9	9	9
8	8	7	6	7	9	6	5
9	7	9	8	6	8	7	4
10	2	5	5	6	8	8	5
11	9	8	8	9	5	5	5
12	9	7	7	8	8	8	8
	No changes made	No changes made	These outcomes have been merged into one new outcome				No changes made

Section 2: Outcomes for Round 2

1. Uptake of partner screening

For studies where RGCS is offered sequentially (one reproductive partner screened first, followed by the other partner only if there is a carrier finding reported), studies should report the number of patients who elect to test their reproductive partner when they are found to be a carrier of a recessive condition.

Summary of Round 1 rankings per group:

6.1 Uptake of partner screening
The **mean** (average) of the rankings for this outcome was **7.0** in the patient group and **7.3** in the health professionals group
The **median** (mid-point) of the rankings for this outcome was **8** in both groups
The **range** of rankings was **2-9**

Limited importance			**Important, but not critical**			**Critically important**		
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
❍	❍	❍	❍	❍	❍	❍	❍	❍

2. Uptake of prenatal diagnosis

Studies should report the number of patients that accept and decline prenatal diagnosis (CVS or amniocentesis) to determine the genetic status of an at-risk pregnancy following an increased risk result from RGCS.

Summary of Round 1 rankings per group:

6.3 Uptake of prenatal diagnosis
The **mean** (average) of the rankings for this outcome was **6.8** in the patient group and **8.2** in the health professionals group
The **median** (mid-point) of the rankings for this outcome was **7** in the patient group and **9** in the health professionals group
The **range** of rankings was **5-9**

Limited importance			**Important, but not critical**			**Critically important**		
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
❍	❍	❍	❍	❍	❍	❍	❍	❍

3. Barriers and facilitators related to further testing and reproductive decision-making

Barriers and facilitators related to further testing and reproductive decision-making - studies should report the factors influencing reproductive decisions relevant to their study. This includes:

- Uptake of partner testing (for studies with a sequential study design where one reproductive partner is screened first, followed by the other partner only if there is a carrier finding reported)
- Uptake of prenatal diagnosis (CVS or amniocentesis)
- Uptake of IVF with pre-implantation genetic diagnosis.

Summary of Round 1 rankings per group:

6.2 Barrier and facilitators to access and uptake of partner screening	**6.4 Barriers and facilitators to access and uptake of prenatal diagnosis**	**6.5 Barriers and facilitators to access and uptake of IVF/PGD**	**6.6 Barriers and facilitators to patient experience of IVF/PGD**
The **mean** (average) of the rankings for this outcome was **7.2** in the patient group and **7.3** in the health professionals group	The **mean** (average) of the rankings for this outcome was **7.3** in the patient group and **7.5** in the health professionals group	The **mean** (average) of the rankings for this outcome was **7.8** in the patient group and **7.5** in the health professionals group	The **mean** (average) of the rankings for this outcome was **7.2** in the patient group and **7.5** in the health professionals group
The **median** (mid-point) of the rankings for this outcome was **8** in both groups	The **median** (mid-point) of the rankings for this outcome was **8** in the patient group and **9** in the health professionals group	The **median** (mid-point) of the rankings for this outcome was **8** in the patient group and **9** in the health professionals group	The **median** (mid-point) of the rankings for this outcome was **8** in the patient group and **9** in the health professionals group
The **range** of rankings was **3-9**	The **range** of rankings was **3-9**	The **range** of rankings was **3-9**	The **range** of rankings was **3-9**

Limited importance			**Important, but not critical**			**Critically important**		
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
❍	❍	❍	❍	❍	❍	❍	❍	❍

4. Support needs when making reproductive decisions

Studies should report the number of patients that requested sources of additional information, such as support groups or connection with those with lived experience of a genetic condition, to inform their reproductive decisions.

Summary of Round 1 rankings per group:

6.3 Uptake of prenatal diagnosis
The **mean** (average) of the rankings for this outcome was **6.0** in the patient group and **7.5** in the health professionals group
The **median** (mid-point) of the rankings for this outcome was **5** in the patient group and **8** in the health professionals group
The **range** of rankings was **4-9**

One participant comment noted that this outcome may be difficult to reliably capture and may not be feasible to expect of all studies. You may wish to consider this opinion as you re-rate this outcome.

Limited importance			Important, but not critical			Critically important		
1	2	3	4	5	6	7	8	9
❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments

(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

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End of Block: Domain 6 - Further testing and reproductive decision-making

Start of Block: Domain 7 - Pregnancy outcomes

Outcome Domain 7 of 16: Pregnancy outcomes

Results from Round 1

There were **5** outcomes in this domain in Round 1. One outcome was duplicated in another domain, therefore has been excluded here and will be addressed in Domain 16. The remaining 4 outcomes are unchanged from Round 1.

Section 1: Round 1 Rankings

Study ID	7.1 Results of prenatal diagnosis (CVS or amniocentesis)	7.2 Rate of fetal loss following prenatal diagnosis (CVS or amniocentesis)	7.3 Decision to continue or terminate a pregnancy identified to be affected through prenatal diagnosis	7.4 Results of IVF with preimplantation genetic diagnosis (PGD) utilised by increased risk couples in subsequent pregnancies
1	7	2	7	7
2	7	7	6	6
3	5	1	3	1
4	9	2	9	9
5	6	6	8	9
6	8	7	8	7
7	8	9	8	9
8	9	9	9	9
9	9	9	9	9
10	5	5	7	7
11	5	6	7	5
12	8	8	8	8
	No changes were made to these outcomes			

Section 2: Outcomes for Round 2

1. Results of prenatal diagnosis (CVS or amniocentesis)

Studies should report the number of affected pregnancies identified through prenatal diagnosis.

Summary of Round 1 rankings per group:

7.1 Results of prenatal diagnosis (CVS or amniocentesis)
The **mean** (average) of the rankings for this outcome was **7.3** in the patient group and **7.0** in the health professionals group
The **median** (mid-point) of the rankings for this outcome was **8** in the patient group and **4** in the health professionals group
The **range** of rankings was **5-9**

Limited importance			Important, but not critical			Critically important		
1	2	3	4	5	6	7	8	9
❍	❍	❍	❍	❍	❍	❍	❍	❍

2. Rate of fetal loss following prenatal diagnosis (CVS or amniocentesis)

Studies should report the number of pregnancies that miscarried following prenatal diagnosis.

Summary of Round 1 rankings per group:

7.2 Rate of fetal loss following prenatal diagnosis (CVS or amniocentesis)
The **mean** (average) of the rankings for this outcome was **7.7** in the patient group and **4.2** in the health professionals group
The **median** (mid-point) of the rankings for this outcome was **9** in the patient group and **4** in the health professionals group
The **range** of rankings was **1-9**

One participant comment noted that this outcome already has existing research data, and it is difficult to ascertain whether the reason for the miscarriage was procedure related. You may wish to consider this opinion as you re-rate this outcome.

Limited importance			Important, but not critical			Critically important		
1	2	3	4	5	6	7	8	9
❍	❍	❍	❍	❍	❍	❍	❍	❍

3. Decision to continue or terminate a pregnancy identified to be affected through prenatal diagnosis

Studies should report the number of affected pregnancies that were terminated following results of prenatal diagnosis.

Summary of Round 1 rankings per group:

7.3 Decision to continue or terminate a pregnancy identified to be affected through prenatal diagnosis
The **mean** (average) of the rankings for this outcome was **8.0** in the patient group and **6.8** in the health professionals group
The **median** (mid-point) of the rankings for this outcome was **8** in both groups
The **range** of rankings was **3-9**

Limited importance			Important, but not critical			Critically important		
1	2	3	4	5	6	7	8	9
❍	❍	❍	❍	❍	❍	❍	❍	❍

4. Results of IVF with preimplantation diagnosis (PGD) utilised by increased risk couples in subsequent pregnancies

Studies should report the number of unaffected ongoing pregnancies following IVF with PGD.

Summary of Round 1 rankings per group:

7.4 Results of IVF with preimplantation genetic diagnosis (PGD) utilised by increased risk couples in subsequent pregnancies
The **mean** (average) of the rankings for this outcome was **7.8** in the patient group and **6.5** in the health professionals group
The **median** (mid-point) of the rankings for this outcome was **9** in the patient group and **7** in the health professionals group
The **range** of rankings was **1-9**

One participant comment noted that this outcome may be difficult to reliably capture and may not be feasible to expect of all studies. You may wish to consider this opinion as you re-rate this outcome.

Limited importance			Important, but not critical			Critically important		
1	2	3	4	5	6	7	8	9
❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments

(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

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End of Block: Domain 7 - Pregnancy outcomes

Start of Block: Domain 8 - Patient attitudes, perceptions and beliefs related to RGCS

Outcome Domain 8 of 16: Patient attitudes, perceptions and beliefs related to RGCS

Results from Round 1

There were **4** outcomes in this domain in Round 1, three of which have been excluded based on Round 1 rankings. The remaining outcome is unchanged since Round 1.

Section 1: Round 1 Rankings

Study ID	8.1 Patient perception that RGCS will inform their reproductive decisions (at the time of the screening offer)
1	5
2	8
3	7
4	7
5	7
6	9
7	6
8	7
9	7
10	5
11	9
12	9
	No changes were made to this outcome

Section 2: Outcomes for Round 2

1. Patient perception that RGCS will inform their reproductive decisions (at the time of the screening offer)

Studies should report how patients perceive changing their reproductive plans if an increased risk result is returned.

Additional information: This outcome is intended to be measured at the time of consent to screening (pre-test) and would require asking patients how they think they will change their plans if they are found to be at increased risk. This reflects **intended** reproductive decisions. This outcome can then be compared after screening to the **actual** reproductive decisions made by patients.

Summary of Round 1 rankings per group:

8.1 Patient perception that RGCS will inform their reproductive decisions (at the time of the screening offer)
The **mean** (average) of the rankings for this outcome was **7.2** in both groups
The **median** (mid-point) of the rankings for this outcome was **7** in both groups
The **range** of rankings was **5-9**

Limited importance			Important, but not critical			Critically important		
1	2	3	4	5	6	7	8	9
❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments

(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

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End of Block: Domain 8 - Patient attitudes, perceptions and beliefs related to RGCS

Start of Block: Domain 9 - Deliberation and informed choice

Outcome Domain 9 of 16: Deliberation and informed choice

Results from Round 1

There were **5** outcomes in this domain in Round 1, one of which has been excluded based on Round 1 rankings. Scoring was similar between the 4 remaining outcomes related to informed choice. As such, we have merged these outcomes into one new outcome:

Informed choice

Studies should assess whether patients made an informed choice to accept or decline screening.

In ranking this outcome below, consider whether you think the concept of informed choice is important to measure in all studies of RGCS.

Section 1: Round 1 Rankings

Study ID	9.1 Patients had enough information to make an informed choice to accept or decline	9.2 Patients were engaged in the decision-making process	9.3 Patients made an informed choice to accept or decline testing	9.4 Patients demonstrated that their knowledge, attitudes and decision to accept or decline RGCS were congruent
1	4	4	4	3
2	9	8	8	8
3	9	9	9	9
4	7	7	7	7
5	9	9	9	1
6	8	6	8	7
7	4	6	6	6
8	3	3	3	4
9	5	6	7	6
10	5	5	5	5
11	3	3	3	3
12	4	7	7	8
	These outcomes have been merged into one new outcome			

Section 2: Outcomes for Round 2

1. Informed choice

Studies should assess whether patients made an informed choice to accept or decline screening.

Summary of Round 1 rankings per group:

9.1 Patients had enough information to make an informed choice to accept or decline	9.2 Patients were engaged in the decision-making process	9.3 Patients made an informed choice to accept or decline testing	9.4 Patients demonstrated that their knowledge, attitudes and decision to accept or decline RGCS were congruent
The **mean** (average) of the rankings for this outcome was **4.0** in the patient group and **7.7** in the health professionals group	The **mean** (average) of the rankings for this outcome was **5.0** in the patient group and **7.2** in the health professionals group	The **mean** (average) of the rankings for this outcome was **5.2** in the patient group and **7.5** in the health professionals group	The **mean** (average) of the rankings for this outcome was **5.3** in the patient group and **5.8** in the health professionals group
The **median** (mid-point) of the rankings for this outcome was **4** in the patient group and **9** in the health professionals group	The **median** (mid-point) of the rankings for this outcome was **6** in the patient group and **8** in the health professionals group	The **median** (mid-point) of the rankings for this outcome was **6** in the patient group and **8** in the health professionals group	The **median** (mid-point) of the rankings for this outcome was **6** in the patient group and **7** in the health professionals group
The **range** of rankings was **3-9**	The **range** of rankings was **3-9**	The **range** of rankings was **3-9**	The **range** of rankings was **1-9**

Limited importance			Important, but not critical			Critically important		
1	2	3	4	5	6	7	8	9
❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments

(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

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End of Block: Domain 9 - Deliberation and informed choice

Start of Block: Domain 10 - Goals of pre- and post-test genetic counselling

Outcome Domain 10 of 16: Goals of pre- and post-test genetic counselling

Results from Round 1

There were **7** outcomes in this domain in Round 1, one of which has been excluded based on Round 1 rankings. For the 6 remaining outcomes, participant comments indicated that they could be combined since they were addressing the same concept, as such we have merged these into one new outcome:

Goals of pre- and post-test genetic counselling

Studies should report whether patients felt that pre- and post-test genetic counselling met their needs and expectations, including aspects such as:

- *Being presented with a choice to accept or decline*
- *Whether they felt enough information was provided to make choices*
- *Whether the manner of the healthcare provider was empathetic and appropriate*
- *Whether the healthcare provider was accessible*
- *Whether the healthcare provider facilitated an understanding of reproductive choices and encouraged a sense of confidence and empowerment.*

Section 1: Round 1 Rankings

Study ID	10.1 Genetic counselling presented screening and further testing as a choice	10.2 Genetic counselling provided sufficient information to meet patient needs	10.3 Genetic counselling supported informed decision-making	10.4 Genetic counselling provider was knowledgeable and empathetic	10.5 Genetic counselling was accessible	10.6 Genetic counselling promoted reproductive empowerment
1	3	3	4	2	3	3
2	8	8	8	9	9	9
3	9	9	9	9	9	9
4	7	8	8	8	8	8
5	7	6	4	4	9	3
6	7	8	7	6	6	7
7	3	6	7	9	9	9
8	4	4	3	3	6	5
9	8	8	7	6	6	6
10	5	5	5	5	5	5
11	3	3	3	3	8	8
12	8	5	5	5	8	9
	These outcomes have been merged into one new outcome					

Section 2: Outcomes for Round 2

1. Goals of pre- and post-test genetic counselling

Goals of pre- and post-test genetic counselling - studies should report whether patients felt that pre- and post-test genetic counselling met their needs and expectations, including aspects such as:

- Being presented with a choice to accept or decline
- Whether they felt enough information was provided to make choices
- Whether the manner of the healthcare provider was empathetic and appropriate
- Whether the healthcare provider was accessible
- Whether the healthcare provider facilitated an understanding of reproductive choices and encouraged a sense of confidence and empowerment.

Summary of Round 1 rankings per group:

10.1 Genetic counselling presented screening and further testing as a choice	**10.2 Genetic counselling provided sufficient information to meet patient needs**	**10.3 Genetic counselling supported informed decision-making**
The **mean** (average) of the rankings for this outcome was **5.2** in the patient group and **6.8** in the health professionals group	The **mean** (average) of the rankings for this outcome was **5.2** in the patient group and **7.0** in the health professionals group	The **mean** (average) of the rankings for this outcome was **5.0** in the patient group and **6.7** in the health professionals group
The **median** (mid-point) of the rankings for this outcome was **5** in the patient group and **7** in the health professionals group	The **median** (mid-point) of the rankings for this outcome was **5** in the patient group and **8** in the health professionals group	The **median** (mid-point) of the rankings for this outcome was **5** in the patient group and **8** in the health professionals group
The **range** of rankings was **3-9**	The **range** of rankings was **3-9**	The **range** of rankings was **3-9**

10.4 Genetic counselling provider was knowledgeable and empathetic	**10.5 Genetic counselling was accessible**	**10.6 Genetic counselling promoted reproductive empowerment**
The **mean** (average) of the rankings for this outcome was **5.2** in the patient group and **6.3** in the health professionals group	The **mean** (average) of the rankings for this outcome was **7.0** in the patient group and **7.3** in the health professionals group	The **mean** (average) of the rankings for this outcome was **7.0** in the patient group and **6.5** in the health professionals group
The **median** (mid-point) of the rankings for this outcome was **5** in the patient group and **7** in the health professionals group	The **median** (mid-point) of the rankings for this outcome was **7** in the patient group and **9** in the health professionals group	The **median** (mid-point) of the rankings for this outcome was **7** in the patient group and **8** in the health professionals group
The **range** of rankings was **2-9**	The **range** of rankings was **3-9**	The **range** of rankings was **3-9**

Limited importance			Important, but not critical			Critically important		
1	2	3	4	5	6	7	8	9
❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments

(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

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End of Block: Domain 10 - Goals of pre- and post-test genetic counselling

Start of Block: Domain 11 - Knowledge and understanding

Outcome Domain 11 of 16: Knowledge and understanding

Results from Round 1

There were **3** outcomes in this domain in Round 1. Minor wording change was made to one outcome to reflect the study design that it is relevant to. No changes were made to the remaining outcomes.

Section 1: Round 1 Rankings

Study ID	11.1 Patient understanding of RGCS	11.2 Recall of screening result at a later timepoint	11.3 Barriers and facilitators influencing patient understanding of RGCS
1	4	5	3
2	9	9	9
3	7	6	9
4	8	5	6
5	4	9	7
6	7	7	9
7	7	3	5
8	4	4	4
9	8	7	7
10	5	1	5
11	3	5	3
12	8	4	7
	No changes made	Minor wording changes were made to this outcome	No changes made

Section 2: Outcomes for Round 2

1. Patient understanding of RGCS

Studies should report patient knowledge which may include the role and significance of screening for those without existing family history or other prior increased risk, the range of conditions included in screening and possible results that can be returned, and options to consider if an increased risk result is received.

Summary of Round 1 rankings per group:

11.1 Patient understanding of RGCS
The **mean** (average) of the rankings for this outcome was **5.8** in the patient group and **6.5** in the health professionals group
The **median** (mid-point) of the rankings for this outcome was **6** in the patient group and **7** in the health professionals group
The **range** of rankings was **3-9**

Limited importance			Important, but not critical			Critically important		
1	2	3	4	5	6	7	8	9
❍	❍	❍	❍	❍	❍	❍	❍	❍

2. Recall of screening result at a later timepoint

Studies that follow up patients over time (longitudinal design) should report a patients ability to correctly recall their screening result at a future timepoint.

Summary of Round 1 rankings per group:

11.2 Recall of screening result at a later timepoint
The **mean** (average) of the rankings for this outcome was **4.0** in the patient group and **6.8** in the health professionals group
The **median** (mid-point) of the rankings for this outcome was **4** in the patient group and **7** in the health professionals group
The **range** of rankings was **1-9**

Limited importance			Important, but not critical			Critically important		
1	2	3	4	5	6	7	8	9
❍	❍	❍	❍	❍	❍	❍	❍	❍

3. Barriers and facilitators influencing patients understanding of RGCS

Studies should report factors that influence patient understanding of RGCS, including aspects such as having access to a knowledgeable provider, methods of education prior to screening, and access to written/visual information.

Summary of Round 1 rankings per group:

11.3 Barriers and facilitators to patient understanding of RGCS
The **mean** (average) of the rankings for this outcome was **5.2** in the patient group and **7.2** in the health professionals group
The **median** (mid-point) of the rankings for this outcome was **5** in the patient group and **8** in the health professionals group
The **range** of rankings was **3-9**

Limited importance			Important, but not critical			Critically important		
1	2	3	4	5	6	7	8	9
❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments

(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

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End of Block: Domain 11 - Knowledge and understanding

Start of Block: Domain 12 - Psychological wellbeing

Outcome Domain 12 of 16: Psychological wellbeing

Results from Round 1

There were **7** outcomes in this domain in Round 1, one of which has been excluded based on Round 1 rankings. No changes have been made to the 6 remaining outcomes.

Section 1: Round 1 Rankings

Study ID	12.1 Anxiety	12.2 Grief and loss following an increased risk result	12.3 Distress following an increased result	12.4 Uncertainty and resilience in patients following an increased risk result	12.5 Impact of results on patients perception of their own health	12.6 Barriers and facilitators to patients psychological and emotional wellbeing during RGCS
1	5	5	6	6	5	4
2	9	9	9	9	9	9
3	7	7	7	9	9	9
4	8	6	8	6	4	8
5	6	6	6	8	3	4
6	6	6	6	7	6	6
7	9	9	9	9	9	9
8	7	7	5	8	8	7
9	9	9	9	8	8	7
10	6	6	6	6	6	6
11	3	3	3	3	3	3
12	4	5	4	6	7	6
	No changes were made to these outcomes					

Section 2: Outcomes for Round 2

1. Anxiety

Studies should report patient-reported levels of anxiety.

Summary of Round 1 rankings per group:

12.1 Anxiety
The **mean** (average) of the rankings for this outcome was **6.3** in the patient group and **6.8** in the health professionals group
The **median** (mid-point) of the rankings for this outcome was **7** in both groups
The **range** of rankings was **3-9**

Limited importance			Important, but not critical			Critically important		
1	2	3	4	5	6	7	8	9
❍	❍	❍	❍	❍	❍	❍	❍	❍

2. Grief and loss following an increased risk result

Studies should report feelings of grief and loss related to increased risk results that impact a current pregnancy, and/or significantly alter the patients perception of their pregnancy journey in future pregnancies.

Summary of Round 1 rankings per group:

12.2 Grief and loss following an increased risk result
The **mean** (average) of the rankings for this outcome was **6.5** in both groups
The **median** (mid-point) of the rankings for this outcome was **7** in the patient group and **6** in the health professionals group
The **range** of rankings was **3-9**

Limited importance			Important, but not critical			Critically important		
1	2	3	4	5	6	7	8	9
❍	❍	❍	❍	❍	❍	❍	❍	❍

3. Distress following an increased risk result

Studies should report the impact of an increased risk result on the patient from the perspective of the impact of events scale (IES) which defines the result as a traumatic event that may have long lasting impacts on the psychological wellbeing of the patient.

Summary of Round 1 rankings per group:

12.3 Distress following an increased risk result
The **mean** (average) of the rankings for this outcome was **6.0** in the patient group and **7.0** in the health professionals group
The **median** (mid-point) of the rankings for this outcome was **6** in the patient group and **7** in the health professionals group
The **range** of rankings was **3-9**

Limited importance			Important, but not critical			Critically important		
1	2	3	4	5	6	7	8	9
❍	❍	❍	❍	❍	❍	❍	❍	❍

4. Uncertainty and resilience in patients following an increased risk result

Studies should report the burden of uncertainty that patients feel following an increased risk result and their ability to cope with this uncertainty.

Summary of Round 1 rankings per group:

12.4 Uncertainty and resilience in patients following an increased risk result
The **mean** (average) of the rankings for this outcome was **6.7** in the patient group and **7.5** in the health professionals group
The **median** (mid-point) of the rankings for this outcome was **7** in the patient group and **8** in the health professionals group
The **range** of rankings was **3-9**

Limited importance			Important, but not critical			Critically important		
1	2	3	4	5	6	7	8	9
❍	❍	❍	❍	❍	❍	❍	❍	❍

5. Impact of results on patients perception of their own health

Studies should report how the patients perception of their own health may change if identified as a carrier.

Summary of Round 1 rankings per group:

12.5 Impact of results on patients perception of their own health
The **mean** (average) of the rankings for this outcome was **6.8** in the patient group and **6.0** in the health professionals group
The **median** (mid-point) of the rankings for this outcome was **8** in the patient group and **6** in the health professionals group
The **range** of rankings was **3-9**

Limited importance			Important, but not critical			Critically important		
1	2	3	4	5	6	7	8	9
❍	❍	❍	❍	❍	❍	❍	❍	❍

6. Barriers and facilitators to patients psychological and emotional wellbeing during RGCS

Studies should report factors directly related to RGCS that can be beneficial or detrimental to a patients emotional wellbeing, including aspects such as feeling informed and able to ask questions, or conversely feeling rushed or not given time for decisions.

Summary of Round 1 rankings per group:

12.6 Barriers and facilitators to patients psychological and emotional wellbeing during RGCS
The **mean** (average) of the rankings for this outcome was **6.3** in the patient group and **6.7** in the health professionals group
The **median** (mid-point) of the rankings for this outcome was **7** in both groups
The **range** of rankings was **3-9**

Limited importance			**Important, but not critical**			**Critically important**		
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments

(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

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End of Block: Domain 12 - Psychological wellbeing

Start of Block: Domain 13 - Decision satisfaction and regret

Outcome Domain 13 of 16: Decision satisfaction and regret

Results from Round 1

There were **2** outcomes in this domain in Round 1. Ranking was similar between both of these outcomes in Round 1. As such, we have merged these into one outcome:

Decisional satisfaction or regret related to RGCS

Studies following up patients over time (longitudinal design) should report longitudinal assessment of patients satisfaction or regret associated with their decision to accept or decline RGCS, and associated with decisions they made based on RGCS results such as undertaking prenatal diagnosis, terminating an affected pregnancy, or accessing IVF.

Section 1: Round 1 Rankings

Study ID	13.1 Retrospective satisfaction with the decision to accept or decline RGCS	13.2 Decisional regret associated with decisions made based on RGCS results
1	4	4
2	7	7
3	4	5
4	8	8
5	6	6
6	7	7
7	9	9
8	9	9
9	7	6
10	6	6
11	3	3
12	5	7
	These outcomes were merged into one new outcome	

Section 2: Outcomes for Round 2

1. Decisional satisfaction or regret related to RGCS

Studies following up patients over time (longitudinal design) should report assessment of patients satisfaction or regret associated with their decision to accept or decline RGCS, and associated with decisions they made based on RGCS results such as undertaking prenatal diagnosis, terminating an affected pregnancy, or accessing IVF.

Summary of Round 1 rankings per group:

13.1 Retrospective satisfaction with the decision to accept or decline RGCS	13.2 Decisional regret associated with RGCS
The **mean** (average) of the rankings for this outcome was **6.5** in the patient group and **6.0** in the health professionals group	The **mean** (average) of the rankings for this outcome was **6.7** in the patient group and **6.2** in the health professionals group
The **median** (mid-point) of the rankings for this outcome was **7** in both groups	The **median** (mid-point) of the rankings for this outcome was **7** in both groups
The **range** of rankings was **3-9**	The **range** of rankings was **3-9**

Limited importance			Important, but not critical			Critically important		
1	2	3	4	5	6	7	8	9
❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments

(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

_____

_____

End of Block: Domain 13 - Decision satisfaction and regret

Start of Block: Domain 14 - Patient satisfaction with the processes of RGCS

Outcome Domain 14 of 16: Patient satisfaction with the processes of RGCS

Results from Round 1

There were **3** outcomes in this domain in Round 1, one of which has been excluded based on Round 1 rankings. No changes were made to the remaining 2 outcomes.

Section 1: Round 1 Rankings

Study ID	14.1 Satisfaction with accessibility, cost and convenience of the screening process	14.2 Satisfaction that information needs have been met
1	3	5
2	7	7
3	7	9
4	7	7
5	5	7
6	8	7
7	7	8
8	7	6
9	8	7
10	6	6
11	9	3
12	7	5
	No changes were made to these outcomes	

Section 2: Outcomes for Round 2

1. Satisfaction with accessibility, cost and convenience of the screening process

Studies should report patients concerns regarding accessibility, cost and convenience of accessing RGCS.

Summary of Round 1 rankings per group:

14.1 Satisfaction with accessibility, cost and convenience of the screening process
The **mean** (average) of the rankings for this outcome was **7.3** in the patient group and **6.2** in the health professionals group
The **median** (mid-point) of the rankings for this outcome was **7** in both groups
The **range** of rankings was **3-9**

Limited importance			Important, but not critical			Critically important		
1	2	3	4	5	6	7	8	9
❍	❍	❍	❍	❍	❍	❍	❍	❍

2. Satisfaction that information needs have been met

Studies should report patient satisfaction with information and education that was provided during RGCS.

Summary of Round 1 rankings per group:

14.2 Satisfaction that information needs have been met
The **mean** (average) of the rankings for this outcome was **5.8** in the patient group and **7.0** in the health professionals group
The **median** (mid-point) of the rankings for this outcome was **6** in the patient group and **7** in the health professionals group
The **range** of rankings was **3-9**

Limited importance			Important, but not critical			Critically important		
1	2	3	4	5	6	7	8	9
❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments

(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

End of Block: Domain 14 - Patient satisfaction with the processes of RGCS

Start of Block: Domain 15 - Familial implications

Outcome Domain 15 of 16: Familial implications

Results from Round 1

There were **4** outcomes in this domain in Round 1, three of which have been excluded based on Round 1 rankings. No changes have been made to the remaining outcome.

Section 1: Round 1 Rankings

Study ID	15.1 Impact of results on a couple's relationship
1	3
2	5
3	6
4	7
5	8
6	6
7	9
8	7
9	7
10	6
11	5
12	8
	No changes were made to this outcome

Section 2: Outcomes for Round 2

1. Impact of results on a couple's relationship

Studies should report how patients perceive that RGCS has impacted their relationship with their reproductive partner, which may include strengthening or strain on the relationship.

Summary of Round 1 rankings per group:

15.1 Impact of results on a couple's relationship
The **mean** (average) of the rankings for this outcome was **7.0** in the patient group and **5.8** in the health professionals group
The **median** (mid-point) of the rankings for this outcome was **7** in the patient group and **6** in the health professionals group
The **range** of rankings was **3-9**

Limited importance			Important, but not critical			Critically important		
1	2	3	4	5	6	7	8	9
❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments

(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

End of Block: Domain 15 - Familial implications

Start of Block: Domain 16 - Perceived utility of RGCS

Outcome Domain 16 of 16: Perceived utility of RGCS

Results from Round 1

There were **3** outcomes in this domain in Round 1, one of which has been excluded based on Round 1 rankings. Minor wording changes were made to one outcome based on participant comments in Round 1.

Section 1: Round 1 Rankings

Study ID	16.1 Reproductive empowerment	16.2 Affected individuals born to patients that accessed RGCS
1	5	6
2	9	4
3	6	6
4	7	7
5	8	9
6	8	7
7	5	9
8	7	7
9	7	8
10	5	7
11	9	9
12	8	8
	No changes were made to this outcome	Minor wording changes were made to this outcome

Section 2: Outcomes for Round 2

1. Reproductive empowerment

Studies should report how empowered patients felt to make reproductive decisions that are right for them following RGCS.

Summary of Round 1 rankings per group:

16.1 Reproductive empowerment
The **mean** (average) of the rankings for this outcome was **6.8** in the patient group and **7.2** in the health professionals group
The **median** (mid-point) of the rankings for this outcome was **7** in the patient group and **8** in the health professionals group
The **range** of rankings was **5-9**

Limited importance			Important, but not critical			Critically important		
1	2	3	4	5	6	7	8	9
❍	❍	❍	❍	❍	❍	❍	❍	❍

2. Affected individuals born to patients that accessed RGCS

Studies that follow up patients over time (longitudinal design) should report on the number of affected individuals born to patients that accessed RGCS. This may be because parents chose to proceed with a pregnancy known to be affected, may have been aware of increased risk but chose not to test during the pregnancy, or because of a laboratory error that missed identifying an increased risk.

Summary of Round 1 rankings per group:

16.2 Affected individuals born to patients that accessed RGCS
The **mean** (average) of the rankings for this outcome was **8.3** in the patient group and **6.5** in the health professionals group
The **median** (mid-point) of the rankings for this outcome was **9** in the patient group and **7** in the health professionals group
The **range** of rankings was **4-9**

Limited importance			Important, but not critical			Critically important		
1	2	3	4	5	6	7	8	9
❍	❍	❍	❍	❍	❍	❍	❍	❍

Comments

(Please refer to each outcome that you are commenting on by number to ensure that we understand which outcome your comment relates to)

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_____

End of Block: Domain 16 - Perceived utility of RGCS

Start of Block: Consent to submit

Our sincerest thanks for your time participating in this Delphi survey. Please ensure you select submit below to ensure your responses are recorded.

Based on the amount of consensus following Round 2, we will decide if we need a Round 3 to further explore opinions on these outcomes. We will reach out with information regarding Round 3 if it is needed.

End of Survey

Supplementary material D.11: List of outcomes per tier following Round 2

Outcome ID and description	Outcome details
Tier 1	
1. Carrier and couple detection rates	Carrier and couple detection rates – studies should report the number of heterozygous carriers identified and/or the number of increased risk couples identified as appropriate for the study design
5. Uptake of post-test genetic counselling	Uptake of post-test genetic counselling for increased risk couples - for studies where RGCS is offered by a non-genetics health professional (GP, midwife or maternal fetal specialist), studies should report the number of increased risk couples that accepted an offer of post-test counselling with a genetic health professional (genetic counsellor or clinical geneticist).
6.1 Uptake of partner testing	Uptake of partner testing – For studies where RGCS is offered sequentially (one reproductive partner screened first, followed by the other partner only if there is a carrier finding reported), studies should report the number of patients who elect to test their reproductive partner when they are found to be a carrier of a recessive condition.
6.2 Uptake of prenatal diagnosis	Uptake of prenatal diagnosis – studies should report the number of patients that accept and decline prenatal diagnosis (CVS or amniocentesis) to determine the genetic status of an at-risk pregnancy following an increased risk result from RGCS.
6.5 Reproductive decisions following an increased risk result	Reproductive decisions following an increased risk result – studies should report the reproductive decisions made by patients based on RGCS, including the decision to continue or terminate a pregnancy determined to be affected through prenatal diagnosis, uptake of IVF with PGD in future pregnancies, decision to proceed with natural conception and test future pregnancies, the decision to not have children or have a smaller family than initially planned, use of an egg or sperm donor.
7.3 Decision to continue or terminate a pregnancy identified to be affected through prenatal diagnosis	Decision to continue or terminate a pregnancy identified to be affected through prenatal diagnosis – studies should report the number of affected pregnancies that were terminated following results of prenatal diagnosis.
16.1 Reproductive empowerment	Reproductive empowerment – studies should report how empowered patients felt to make reproductive decisions that are right for them following RGCS.
16.2 Affected individuals born to patients that accessed RGCS	Affected individuals born to patients that accessed RGCS – studies should report on the number of affected individuals born to patients that accessed RGCS. This may be because parents chose to proceed with a pregnancy known to be affected, may have been aware of increased risk but chose not to test during the pregnancy, or because of a laboratory error that missed identifying an increased risk.

Tier 2	
6.3 Barriers and facilitators related to further testing and reproductive decision	Barriers and facilitators related to further testing and reproductive decision-making - studies should report the factors influencing reproductive decisions relevant to their study. This includes: Uptake of partner testing (for studies with a sequential study design where one reproductive partner is screened first, followed by the other partner only if there is a carrier finding reported) Uptake of prenatal diagnosis (CVS or amniocentesis) Uptake of IVF with pre-implantation genetic diagnosis
7.1 Results of prenatal diagnosis (CVS or amniocentesis)	Results of prenatal diagnosis (CVS or amniocentesis) - studies should report the number of affected pregnancies identified through prenatal diagnosis.
8. Patient perception that RGCS will inform their reproductive decisions (at the time of the screening offer)	Patient perception that RGCS will inform their reproductive decisions (at the time of the screening offer) - studies should report how patients perceive changing their reproductive plans if an increased risk result is returned.
12.3 Distress following an increased risk result	Distress following an increased risk result - studies should report the impact of an increased risk result on the patient from the perspective of the impact of events scale (IES) which defines the result as a traumatic event that may have long lasting impacts on the psychological wellbeing of the patient.
14.1 Satisfaction with accessibility, cost and convenience of the screening process	Satisfaction with accessibility, cost and convenience of the screening process - studies should report patients concerns regarding accessibility, cost and convenience of accessing RGCS.
Tier 3	
4.1 Uptake of RGCS	Uptake of RGCS - studies should report an appropriate outcome to capture uptake within the scope of their study design. This includes: The number of patients offered RGCS; the number of patients that accept; where the two previous outcomes are not available, the number of screening tests conducted may be used as a proxy for uptake.
6.4 Support needs when making reproductive decisions	Support needs when making reproductive decisions - studies should report the number of patients that requested sources of additional information, such as support groups or connection with those with lived experience of a genetic condition, to inform their reproductive decisions.
7.4 Results of IVF with preimplantation diagnosis (PGD) utilised by increased risk couples in subsequent pregnancies	Results of IVF with preimplantation diagnosis (PGD) utilised by increased risk couples in subsequent pregnancies - studies should report the number of unaffected ongoing pregnancies following IVF with PGD.

9. Informed choice	Informed choice - studies should assess whether patients made an informed choice to accept or decline screening
11.1 Patient understanding of RGCS	Patient understanding of RGCS - studies should report patient knowledge which may include the role and significance of screening for those without existing family history or other prior increased risk, the range of conditions included in screening and possible results that can be returned, and options to consider if an increased risk result is received.
11.3 Barriers and facilitators influencing patients understanding of RGCS	Barriers and facilitators influencing patients understanding of RGCS - studies should report factors that influence patient understanding of RGCS, including aspects such as having access to a knowledgeable provider, methods of education prior to screening, and access to written/visual information.
12.4 Uncertainty and resilience in patients following an increased risk result	Uncertainty and resilience in patients following an increased risk result - studies should report the burden of uncertainty that patients feel following an increased risk result and their ability to cope with this uncertainty.
14.2 Satisfaction that information needs have been met	Satisfaction that information needs have been met - studies should report patient satisfaction with information and education that was provided during RGCS.
15. Impact of results on a couple's relationship	Impact of results on a couple's relationship - studies should report how patients perceive that RGCS has impacted their relationship with their reproductive partner, which may include strengthening or strain on the relationship.
Tier 4	
2. Identification of secondary or incidental findings	Identification of secondary or incidental findings - studies should report any results that were secondary to the primary carrier screening results, including the number of variants of uncertain significance if reported back to patients, or the number of homozygous, hemizygous or compound heterozygous findings that indicate that a healthy prospective parent undertaking RGCS is at risk or affected with one of the screened conditions
3. Technical laboratory outcomes	Technical laboratory outcomes - studies should report any technical laboratory outcomes that impact on the patient experience of RGCS and/or on the interpretation of results. This includes: laboratory errors that lead to the incorrect interpretation of results, such as sampling or contamination errors, false negatives, or false positives; the rate of test failure as a result of insufficient or poor-quality DNA
4.2 Barriers and facilitators to access and uptake of RGCS	Barriers and facilitators to access and uptake of RGCS - studies should report patient perception of the accessibility of RGCS and how this influences their decision to have it. Accessibility includes aspects such as cost and convenience of the process.
11.2 Recall of screening result at a later timepoint	Recall of screening result at a later timepoint - studies should report a patients ability to correctly recall their screening result at a future timepoint.
12.1 Anxiety	Anxiety - studies should report patient reported levels of anxiety.

12.2 Grief and loss following an increased risk result	Grief and loss following an increased risk result - studies should report feelings of grief and loss related to increased risk results that impact a current pregnancy, and/or significantly alter the patients perception of their pregnancy journey in future pregnancies.
12.5 Impact of results on patients perception of their own health	Impact of results on patients perception of their own health - studies should report how the patients perception of their own health may change if identified as a carrier.
12.6 Barriers and facilitators to patients psychological and emotional wellbeing during RGCS	Barriers and facilitators to patients psychological and emotional wellbeing during RGCS - studies should report factors directly related to RGCS that can be beneficial or detrimental to a patients emotional wellbeing, including aspects such as feeling informed and able to ask questions, or conversely feeling rushed or not given time for decisions.
13. Decisional satisfaction or regret related to RGCS	Decisional satisfaction or regret related to RGCS - studies should report longitudinal (long-term) assessment of patients satisfaction or regret associated with their decision to accept or decline RGCS, and associated with decisions they made based on RGCS results such as undertaking prenatal diagnosis, terminating an affected pregnancy, or accessing IVF
No agreement	
7.2 Rate of fetal loss following prenatal diagnosis (CVS or amniocentesis)	Rate of fetal loss following prenatal diagnosis (CVS or amniocentesis) - studies should report the number of pregnancies that miscarried following prenatal diagnosis.