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:

- Dr Chris Jacobs
- A/Prof Alison McEwen
- A/Prof Toby Newton-John

University of Technology Sydney
Graduate School of Health, Faculty of Health

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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.

This research is supported by a UTS Research Excellence Scholarship.

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Ebony Richardson

Date: 21/12/2022

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.

Acknowledgements

Although a PhD is a journey embarked upon by an individual, it is by no means a solo undertaking. The hands and minds of many people have contributed to this body of work, and I am grateful to everyone who has supported me along the way.

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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

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

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

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*.

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
- Contribution of Dr Ashley Crook: joint author
- Contribution of Dr Karine Manera: joint author

Signatures:

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Ebony Richardson

Production Note:
Signature removed prior to publication.

Dr Chris Jacobs

Production Note:
Signature removed prior to publication.

A/Prof Alison McEwen

Production Note:
Signature removed prior to publication.

Prof Toby Newton-John

Production Note:
Signature removed prior to publication.

Dr Ashley Crook

Production Note:
Signature removed prior to publication.

Dr Karine Manera

Dissemination of research

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Richardson E (2021) Results of a systematic review and protocol for further projects. Paper presented at: UTS Faculty of Health conference; November 24th, 2021; Sydney, Australia.

Accepted for poster presentation – peer reviewed

Richardson E, McEwen A, Newton-John T, Manera K, Crook A, Jacobs C. (2020) The Core Outcome Development for Carrier Screening (CODECS) Study: Systematic review of outcomes in studies implementing reproductive genetic carrier screening. Paper presented at: Human Society of Australasia (HGSA) annual scientific meeting; November 24th, 2020; Virtual conference.

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.

Richardson E, McEwen A, Newton-John T, Crook A, Jacobs C. (2021) Incorporating the patient perspective: Systematic review of outcomes in qualitative studies evaluating the patient experience of reproductive genetic carrier screening. Paper presented at: Human Society of Australasia (HGSA) annual scientific meeting; August 16th, 2021; Adelaide, Australia.

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

Invited oral presentations

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