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Defining core outcomes of reproductive genetic carrier screening: A Delphi survey of Australian and New Zealand stakeholders

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Abstract

Objective: Understanding the value, benefits and harms of health interventions is needed to inform best practice and ensure responsible implementation of new approaches to patient care. Such value is demonstrated through the assessment of outcomes; however, which outcomes are assessed is often highly varied across studies and can hinder the ability to draw robust conclusions. The Core Outcome Development for Carrier Screening study aims to understand the outcomes that can meaningfully capture the value of reproductive genetic carrier screening (RGCS).

Method: The authors report an iterative, two-round online Delphi survey of Australian and New Zealand stakeholders to determine the degree of consensus regarding the core outcomes of RGCS. Panellists 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.

Results: The top tier outcomes represent those agreed to be critically important for all future studies of RGCS to assess 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.

Conclusion: These findings can guide the selection of meaningful outcomes in studies aiming to demonstrate 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.

Key points

What is already known on this topic?

- Determining the value of a health intervention such as reproductive genetic carrier screening (RGCS) relies on the measurement of outcomes that can demonstrate benefits and capture potential harms.

- To date, the outcomes assessed in studies on RGCS have been highly varied and there has been limited involvement of patients and other key stakeholders in determining which outcomes can most meaningfully capture the value of RGCS.

What does this study add?

- This study reports a Delphi consensus process to define a preliminary set of core outcomes of RGCS that should be considered by all future studies.
- Stakeholders supported the consistent reporting of carriers and/or carrier couples, uptake of partner testing and post-test genetic counselling, uptake of prenatal diagnosis and decision-making for affected pregnancies, reproductive decisions made by patients, patient empowerment, and number of affected individuals born to patients that accessed RGCS.

1 | INTRODUCTION

A demonstration of the value of genetic health interventions, including genetic counselling and genetic testing, is needed to inform best practice, guide policy, and funding, and ensure responsible implementation into patient care. The assessment of outcomes that can accurately capture benefits and harms is an important component of demonstrating value.[1,2] A range of outcomes have been reported across the genetics 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] on 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 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 a 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 the 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 programme available broadly to the general population, an understanding of the benefits and potential harms is crucial to ensure 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 the outcomes being assessed in research can meaningfully capture the value of RGCS, increasing the likelihood that research 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 in identifying which outcomes are most informative and appropriate to assess in studies of RGCS.[17] We also found that few studies incorporated patient-reported outcome measures and found no evidence of patient involvement in deciding which outcomes are relevant, leading to a limited representation of the patient perspective. A sequential review of the qualitative literature highlighted 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 COS. 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.

2 | MATERIALS AND METHODS

2.1 | 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 or expertise in RGCS. This study was reported per recommendations from the Core Outcome Measures in Effectiveness Trials initiative.[21] Ethics approval was granted by the University of Technology Sydney Ethics Committee (UTS HREC ETH20-5179).

2.2 | Participant selection

An expert panel of AUS/NZ participants was convened. Participants belonged to two groups; (1) patients who had undertaken RGCS and (2) 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.

2.2.1 | 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]

2.2.2 | 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. 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 min. The importance of committing to the full consensus process was conveyed to the invitees.

2.2.3 | 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 the previously published work, including a systematic review[17,18] that had been published at the time of the Delphi survey.

2.3 | Compiling outcomes

All outcomes identified from the systematic review process[17,18] and qualitative interviews with patient stakeholders[19] were compiled into a list comprising 175 outcomes across 25 outcome domains. Each outcome domain was reviewed by the 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 1).

2.4 | 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 patients 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.

2.5 | Data collection

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

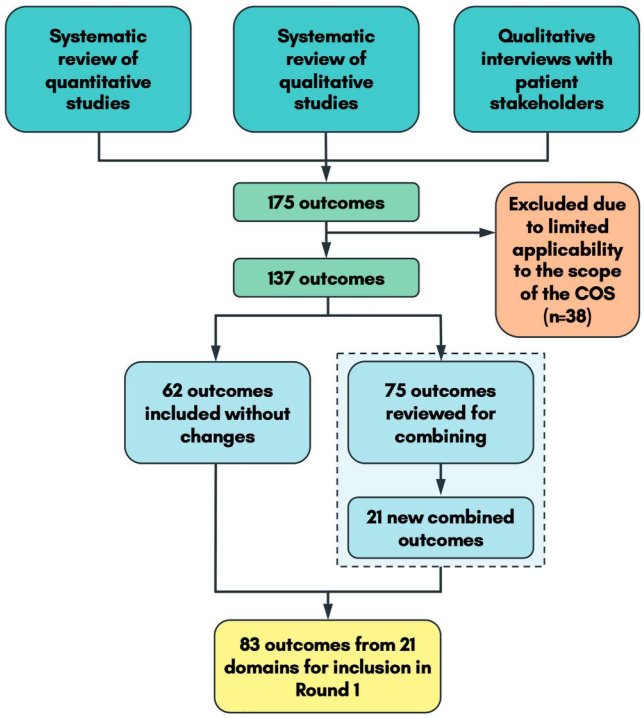

FIGURE 1 Compiling outcomes for inclusion in Round 1. [Colour figure can be viewed at wileyonlinelibrary.com]

2.5.1 | Round 1

The Round 1 survey was available to participants for 4 weeks (January–February 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 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.

2.5.2 | 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.

2.6 | Data analysis

2.6.1 | 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. 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 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 the participant group or ≥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.

2.6.2 | 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.

2.6.3 | 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. The ER prepared all outcomes that reached the threshold for inclusion in Round 2 and presented these to the SMG for agreement.

2.6.4 | Quantitative analysis

The mean, median and proportion of participants who rated the outcome as critically important (7–9) 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.

3 | RESULTS

3.1 | Participant characteristics

A summary of the participants is provided in Table 1. Round 1 was completed by 12 participants, seven from Australia and five from NZ. Equal representation was obtained between the patients 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 foetal 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 1 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[a])	
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%)

[a]Some participants had multiple areas of expertise.

3.2 | Distribution of rankings from Round 1 and inclusion in Round 2

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

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 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. Full outcome details are available in the Supporting Information S1. The distributions of rankings for each outcome are shown in Figure 3.

3.3 | 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 3. All outcomes in Round 2 were ranked either "important but not critical" or "critically important" by one or both

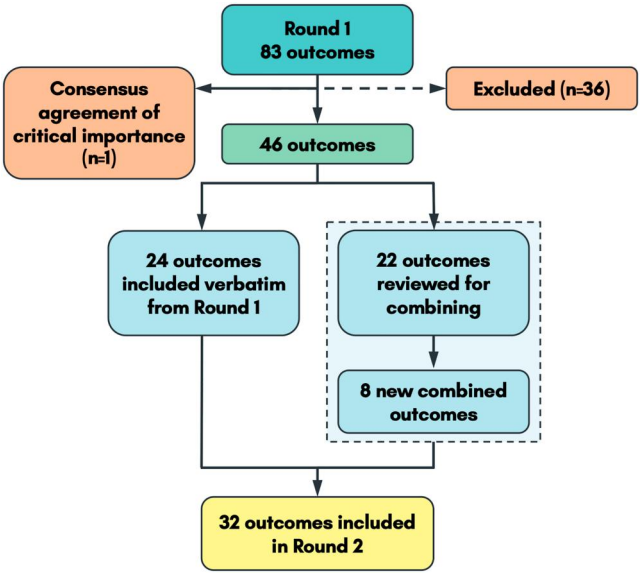

FIGURE 2 Reduction in outcomes based on Round 1 results. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 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 foetal 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

(Continues)

TABLE 2 (Continued)

CODECS outcome domains and outcome descriptions	Patients		Health professionals	
	Mean	Median	Mean	Median
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

TABLE 2 (Continued)

CODECS outcome domains and outcome descriptions	Patients		Health professionals	
	Mean	Median	Mean	Median
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

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

[a]relevant to studies offering RGCS sequentially.

[b]relevant to studies offering RGCS prenatally.

groups of participants. The distributions of rankings are shown in Figure 4 and were used to define tiers representing the degree of consensus regarding the importance of each outcome.

3.4 | 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, 8 outcomes were prioritised and are described in Figure 5.

3.5 | Lower tiers of consensus

A list of all outcomes per tier is available in the Supporting Information S1.

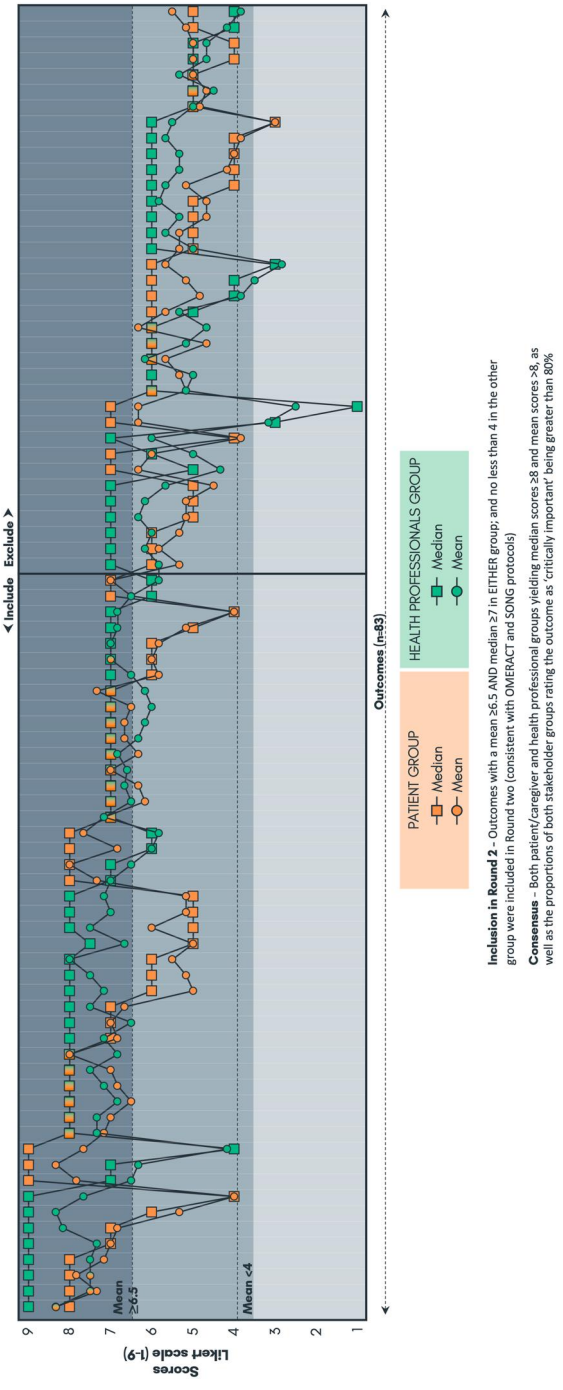

FIGURE 3 Distribution of rankings from Round 1. Vertical columns show the mean and median for each of the 83 outcomes; values for the patient group are indicated in orange and health professional groups in green. Mean thresholds are shown to assist with the interpretation. Per the defined criteria, outcomes with a mean ≥ 6.5 and median ≥7 from either the participant group or ≥4 in the other group were included in Round 2. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 3 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 foetal 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

(Continues)

TABLE 3 (Continued)

CODECS outcome domains and outcome descriptions	Patient group		Health professionals group	
	Mean	Median	Mean	Median
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

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

[a]relevant to specific study designs.

[b]relevant to studies offering RGCS prenatally.

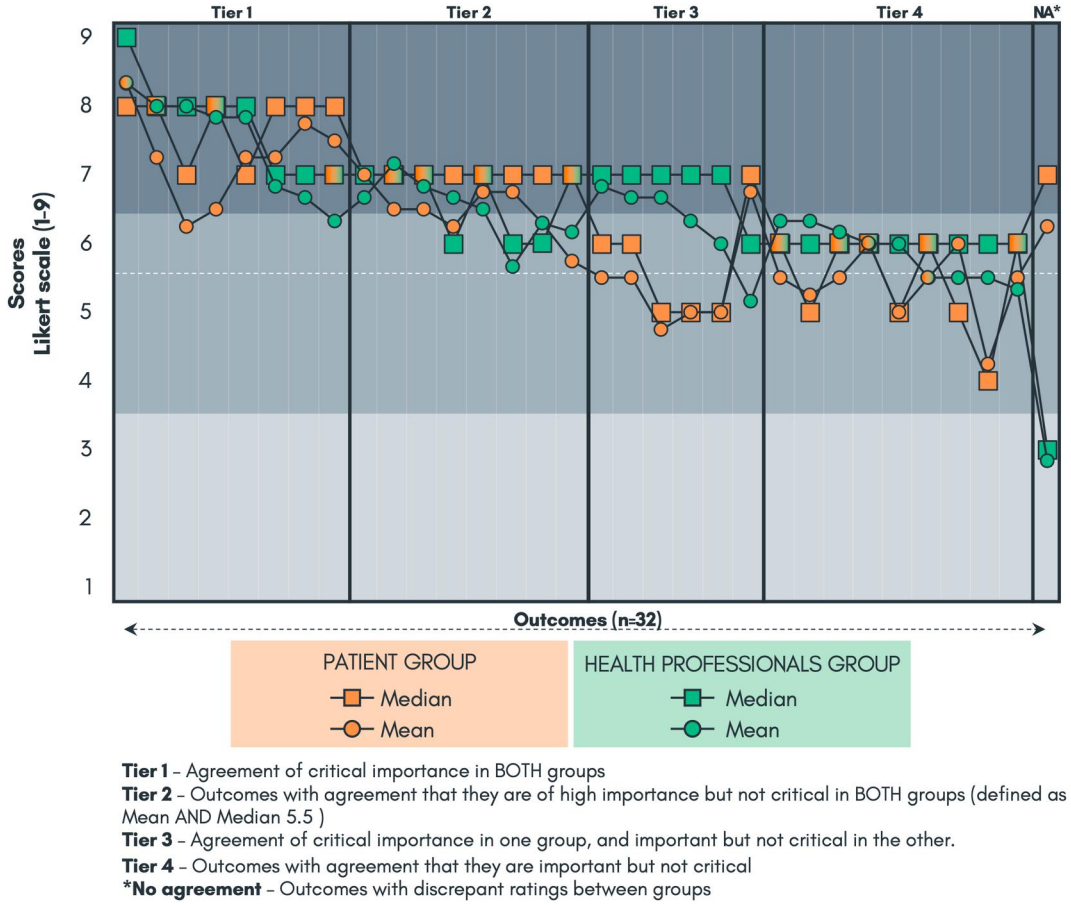

FIGURE 4 Distribution of rankings in Round 2. Vertical columns show the mean and median for each of the 32 outcomes; values for the patient group are indicated in orange and health professional groups in green. [Colour figure can be viewed at wileyonlinelibrary.com]

3.5.1 | Tier 2

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

3.5.2 | Tier 3

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

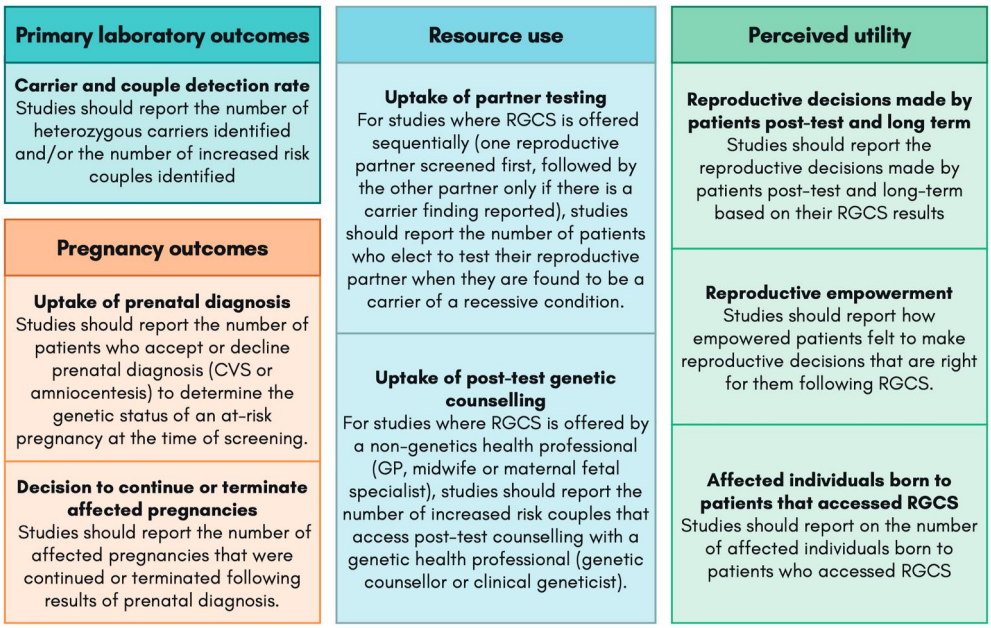

FIGURE 5 Preliminary COS. Defined by Tier 1 outcomes that reached consensus on critical importance. [Colour figure can be viewed at wileyonlinelibrary.com]

3.5.3 | Tier 4

Nine outcomes were grouped into 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.

3.6 | Outcomes with no agreement

One outcome "rate of foetal loss following prenatal diagnosis (CVS or amniocentesis)" was discordant between the 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 foetal loss. Without this broader context, patients understandably considered this a critical outcome.

4 | 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.

The first outcome domain prioritised in this Delphi survey was "primary laboratory outcomes." Consistent reporting of primary laboratory outcomes is needed for comparison between studies and to provide empirical evidence to guide best practice; however, which outcome to report will differ dependent on the approach to screening. Different schools of thought favour either (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. Firstly, 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 having 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 the 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 guide how RGCS is offered in the future and whether additional support is needed for patients accessing RGCS in the prenatal period.

Participants also prioritised outcomes related to resource use, which is a crucial element of scaling RGCS to a population screening offer. Current recognised resource limitations in the genetics workforce are a key element of scaling and a lack of specially trained genetic counsellors necessitates the use of non-genetics health professionals as alternative providers to offer RGCS, reserving the specialised genetic workforce for management of 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 offering RGCS.[36] Studies in this review 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 min 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 build evidence for increased resource allocation.

The goals of RGCS describe its intended benefits and are captured through the measurement of outcomes that assess utility. The goals of RGSC are conceptualised in various ways in the literature and perspectives have evolved over time on how to frame them most appropriately. Early RGCS screening programs measured utility based on the prevention of genetic conditions and reduction in disease incidence, likely attributable to the focus on increased risk groups that are disproportionately affected by certain genetic conditions.[11,41,42] However, recent discussions have questioned the ethical appropriateness of such outcomes 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. Participants in this study prioritised the outcome "affected births" in the preliminary COS. 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 to minimise potential harms from a bioethical perspective.

The goal to facilitate reproductive autonomy and enable informed reproductive decision-making has been more recently focused on as an appropriate goal of RGCS.[45,46] However, it remains unclear how best to assess the utility of RGCS for reproductive decision-making. A common approach 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 metric of behaviour alone. Our previous work highlighted 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] The participants in this study 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 programme will be a continued focus of the CODECS study in the next stages of the consensus process to define a final COS.

5 | LIMITATIONS

This Delphi survey was limited to the Australian and NZ 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. With 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 given 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 | CONCLUSION

The outcomes reported herein reflect the perspective of AUS/NZ stakeholders regarding the core outcomes of RGCS that should be reported in all future 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 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]

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CONFLICT OF INTEREST STATEMENT

No conflicts to disclose.

DATA AVAILABILITY STATEMENT

Data generated as part of this study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

This study received ethics approval from The University of Technology Sydney Ethics Committee (UTS HREC ETH20-5179). The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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