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Economic Evaluation of Reproductive Carrier Screening for Recessive Genetic Conditions: A Systematic Review

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ABSTRACT

Introduction: Autosomal recessive (AR) and x-linked (XL) conditions are rare but collectively common which impact millions of people globally on morbidity, mortality and costs. Advanced medical technologies allow prospective parents to make informed reproductive decisions to avoid having affected children. Economic evaluations targeting on reproductive carrier screening (RCS) for AR and/or XL conditions have been conducted, but there has not been a systematic review in this area.

Areas covered: A systematic search of economic evaluations for RCS was undertaken using the following databases – EMBASE, MEDLINE and SCOPUS. The search strategy was designed to capture full economic evaluations related to RCS since 1990. This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) strategy. The included 23 studies adopted various types of methodologies to conduct economic evaluations. The majority of studies examined a single condition. The various clinical strategies and screened conditions caused the different cost-effectiveness conclusions in the published studies.

Expert opinion: Establishing a validated and practical clinical strategy of RCS and investigating the cost-effectiveness of multiple conditions in one economic evaluation are critical for implementing RCS in the future. Further economic evaluations are essential to provide evidence-based practice for decision-makers.

Article Highlights

- This is the first systematic review which critically assesses the economic evaluations of reproductive carrier screening including multiple genetic conditions. Most included studies were of high quality as per Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.

- Economic evaluations of reproductive carrier screening have been conducted using various analytical approaches and cost-effectiveness thresholds. Although examining single condition accounted for the majority of the published studies, assessing multiple conditions in one economic evaluation raised more concern recently because of the advanced medical technologies. The various clinical strategies and screened conditions caused the different cost-effectiveness conclusions in the published studies.

- The findings in this review provide useful information to assist policy makers when implementing carrier screening program. This review also provides a comprehensive summary of the existing studies, which can help further research in this area.

1. Introduction

Mendelian conditions have major impacts on health budgets, hospital systems and society at large. Although individually rare [1], collectively they are common and affect millions of people globally [2], accounting for around one in five infant deaths [3]. Approximately 1-2% of couples have a high risk of having a child affected by a recessive genetic condition, and around one in 400 children will be born with a recessive condition [4]. It is estimated that on average, people are carriers for three severe recessive conditions [5].

Autosomal recessive (AR) and x-linked (XL) conditions can have impacts on families and individuals across multiple domains, including physical and psychological health as well as increased direct costs of healthcare and associated costs (such as the cost of home modifications for people with a physical disability). Spinal muscular atrophy (SMA) is an example of an AR condition, presenting with progressive muscle weakness and atrophy due to loss of anterior horn cells. In SMA type I, median survival is less than 12 months, with associated grief and other psychological impacts for families [6]. A new genetic therapy for SMA was approved by the US Food and Drug Administration (FDA) in May 2019, ZOLGENSMA® (Onasemnogene abeparvovec); a one-time injection for affected children less than two years old [7]. However, its price is US $2.125 million per dose [8] which is unaffordable to the vast majority of families. In addition to this, SPINRAZA® (Nusinersen) was approved in 2016 by US FDA as a treatment for SMA and the price is estimated to be US $750,000 in the first year and US $375,000 annually thereafter [9]. While these costs

are particularly high, SMA is far from being the only example of an AR or XL condition for which expensive targeted therapies are currently available or are becoming available. Examples include the various lysosomal storage disorders for which enzyme replacement therapy is available [10], and cystic fibrosis (CF). Conventional therapies for CF were already burdensome to families and patients, with the requirement for multiple medications, physiotherapy and frequent hospital admissions. New targeted therapies such as elexacaftor–tezacaftor–ivacaftor triple therapy promise improvements in survival and quality of life but at substantial cost [11,12]. There are many other such therapies under development.

In recent years, reproductive carrier screening (RCS) has been widely introduced to identify couples who have a high risk of having children affected by AR or XL conditions. The Israeli RCS program has screened up to 70,000 individuals annually for multiple conditions [13]. The goal of RCS is allowing reproductive autonomy and informed reproductive decision making [14]. There is evidence that couples who are identified as carriers use this information to avoid having affected children, with the effect of reducing the incidence of the screened conditions, such as Tay-Sachs disease [15]. In addition, the technology used in carrier screening has rapidly advanced over recent decades with less waiting time, reduced financial cost and higher sensitivity and specificity [16]. RCS for CF has also been demonstrated to be cost-effective in an Australian study [17]. Many organizations have made recommendations regarding offering RCS, including the American College of Obstetricians and Gynecologists (ACOG) [18], American College of Medical Genetics and Genomics (ACMG) [19], Royal Australian College of General Practitioners (RACGP) [20],

and RANZCOG [21]. However, while RCS is available in many countries, it is usually not a government funded healthcare service [21] with limited exceptions (e.g. beta-thalassemia and sickle cell anemia in the UK) [22], which is considered as a limitation to its uptake [23,24].

Economic evaluation in healthcare is a systematic framework to assess the costs and outcomes of healthcare interventions [25]. It is a tool providing a way of thinking and problem-solving for health planners and policy makers, to allocate limited resources in healthcare systems [26]. Three types of methodologies in full economic evaluations are commonly used, including cost-benefit analysis (CBA), cost-effectiveness analysis (CEA), and cost-utility analysis (CUA) [25]. CBA evaluates the costs and outcomes by using monetary values, whereas CEA measures outcomes as natural units instead. CUA measures costs as monetary units but outcomes as quality-adjusted life years (QALYs) [25], and this method has been recommended in the guidelines of health technology assessment (HTA) in many places such as Europe, Canada and Australia [27-30].

Different types of carrier screening options have been evaluated and reported in the literature, which indicated that these options could incur substantial costs and deliver substantial benefits [31]. In a systematic review [31] to examine economic evaluations of CF screening, 14 studies were identified between 1990 and 2006. The authors concluded that the study design, model inputs, and results of the selected studies were heterogeneous and it was difficult to make comparisons or generalize their results. Due to the technological advances in genetic sequencing in the last decade [32,33], their findings and

conclusions need to be updated, especially as the scope of RCS has expanded beyond the individual condition framework to include genomic panels covering multiple genes.

To our knowledge, a systematic review of economic evaluations in RCS, considering multiple conditions, has not been performed. We conducted a systematic review in order to appraise economic evaluations of carrier screening in AR and XL conditions for couples either in reproductive planning or pregnancy phases. This review will consolidate the existing studies, identify limitations, and seek to establish evidence-based recommendations from a health economic perspective.

2. Methods

2.1 Search strategy

A systematic search of economic evaluations for RCS was undertaken on the 2nd of July 2019 using the following databases – EMBASE, MEDLINE and SCOPUS. This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) strategy [34]. The protocol of this systematic review was registered to PROSPERO (registration number: CRD42020147125). The PICO for this review was:

- **P**opulation: preconception and pregnant couples (i.e. couples with reproductive plan and/or pregnant couples);

- **I**ntervention/**c**omparator: RCS for AR and XL conditions;

- **O**utcome: monetary and health-related outcomes of RCS.

The search was conducted using terms associated with "reproductive", "carrier screening" and "economic evaluation" with appropriate truncation and adjacency (see **Appendix 1** for the full searches in the supplemental materials). When completing this systematic review, we conducted an updated search from 2019 to August of 2020 to identify the up-to-date studies within our interest.

2.2 Study selection

The search strategy was designed to capture full economic evaluations related to RCS since 1990 [31,32], and as such non-economic evaluation studies were excluded [35]. The search was also limited to English language studies. At the title and abstract checking phases, inclusion criteria were limited to AR and XL conditions, reproductive health, and studies in humans. The targeted population groups of this systematic review were preconception and

pregnant couples, so in the full text checking, studies that did not consider these groups as participants were excluded. For example, a recently published CEA of genomic screening was excluded because its targeted population groups were all young adults, rather than preconception or pregnant couples [36]. If both dominant and recessive conditions were discussed in a study, that study was selected, but the results for the dominant conditions were not included. Studies which focused on cascade carrier screening were not included [37]. Excluded studies also consisted of letters, editorials, notes, comments, conference abstracts and non-peer reviewed articles. Detailed inclusion and exclusion criteria are listed in **Appendix 2** of the supplemental materials. The checking process was developed by two authors independently (TW and MB), and any discrepancy was resolved by consensus (with planned arbitration with MD if consensus could not be reached).

2.3 Data extraction and quality assessment

Data extraction and data synthesis were developed from the selected studies using tables. A generic clinical pathway of RCS was developed by incorporating the results from the selected studies, which determined the decision-analytic framework and identified the required modelling inputs. The quality of these economic evaluations was assessed applying the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist [38], a 24 item set of guidelines. Each item was scored either "1" (fully met the specific criterion), "0" (not at all or partially met the criterion), or "NA" (not applicable). The proportions represented the quality of these studies (higher proportion indicating higher quality).

3. Results

3.1 Study characteristics

The initial search yielded a total of 4,308 published studies. After exclusion and checking the reference lists of the selected studies (defined as other sources in PRISMA), 23 studies were included (**Fig. 1**). The updated search yield 645 studies from 2019 to August of 2020 following our searching strategy. Based on our inclusion and exclusion criteria, no new studies were identified. The basic characteristics of the selected studies are categorized and summarized in **Table 1**. More detailed information regarding these studies is presented in **Table S1** of the supplemental materials. There were 11 studies [39-49] published from 1990-1999 and six in each of 2000-2009 [50-55] and 2010-2019 [17,32,33,56-58]. Most of the studies were from the US (n=11, 48%) [32,33,40,43-45,49,51,53,55,56], followed by the Netherlands (n=4, 17%) [46-48,54], and Australia [17,52,57] and the UK [41,42,58] (each n=3, 13%). There were two studies from each of Denmark [50] and Israel [39]. AR conditions were the focus in the majority of the selected studies (n=18, 78%) [17,32,39-46,48,50,51,54-58], and four studies (17%) focused on XL conditions [47,49,52,53]. There was one study (4%) that evaluated screening for both AR and XL conditions [33]. The majority of studies investigated a single condition, namely, CF (n=15, 65%) [17,39-46,48,50,51,54,55,57], Fragile X Syndrome (FXS) (n=4, 17%) [47,49,52,53], SMA (n=1, 4%) [56], and Sickle Cell disease & Thalassemia (SCT) (n=1, 4%) [58]. Two studies (9%) evaluated multiple conditions, which were published in 2016 [32] and 2019 [33] respectively.

3.2 Study design

The selected studies adopted various types of methodologies to conduct economic evaluations, including CBA, CEA and CUA (**Table 1**). Seventeen studies (74%) [17,32,33,39-43,45,48-52,55,57,58] applied a singly analytical type in their analyses (eight for CBA and nine for CEA), while the other six studies used different combinations of these methodologies: three combining CBA and CEA [46,47,54]; one combining CBA and CUA [53]; one combining CEA and CUA [56]; and one combining CBA, CEA and CUA [44]. In regard to the participants, more than half of the selected studies focused on pregnant couples (n=14, 61%) [39-41,43-45,49-53,56-58], and three studies (13%) [33,48,54] focused on the preconception group. There were another five studies (25%) [17,32,42,46,47] that included both groups, whereas one of the 23 studies was for couples but did not record their pregnancy status specifically [55].

According to the aims of these selected studies, different interventions/screening options were considered for the economic evaluation (**Table 1**), including screening timing, screening place/by whom, screening strategy, screening technology, screening policy, and combination of screening options. Examples for each intervention/screening option are listed in **Table 2**. Specifically, the distribution of these interventions/screening options by the year of publication is illustrated in **Figure 2**. In the period of 1995-1999, the number of published studies (n=9) [41-49] and the types of interventions/screening options (N=6) were the largest compared to other periods. The screening policy was selected as one type of intervention/screening options from 1990 to 2014. In the period of 2015-2019, two studies considered screening technology as their interventions/screening options [32,33].

Of the 23 studies, the perspectives consisted of private health insurer (n=1, 4%) [33], health sector (n=8, 35%) [17,32,40-42,45,57,58], third-party payer (n=2, 9%) [51,55], and societal perspective (n=9, 39%) [44,46-49,52-54,56]. Three studies (13%) [39,43,50] were reported to apply more than one perspective. All the studies explicitly defined the data sources of costs, such as published and unpublished data, literature, registries, patients' questionnaires, hospital/institute records and authors' assumptions. All studies clearly reported the unit of currencies that they used. The most frequently used currency was US dollars. With respect to the discount rate, it was not reported in eight of the studies [41-43,45,49,51,55,58]. Of the 15 studies reporting a discount rate, seven studies used 3% [32,33,44,47,48,53,56] and another six used 5% [17,39,40,46,50,52], whereas two studies applied 3.5% [57] and 4% [54] respectively. The detailed economic data of these selected studies are presented in **Table S2** of the supplemental materials.

3.3 Model inputs

A generic clinical pathway of RCS for both preconception and pregnant couples was developed according to the analyses from the selected studies and illustrated in **Figure 3**. The items of probabilities and costs were summarized alongside the screening pathway.

The data of uptake rate in the selected studies were mainly based on authors' assumptions and literature review. The adopted uptake rates of screening for pregnant women/couples ranged from 50% to 100%. When sequential screening strategy was applied and the women's screening results were positive, the partners' uptake rates of screening were from 43% to 85%. For preconception couples, the uptake rates of screening were from 10% to

100%, but the rates were relatively lower compared to pregnant couples. For example, three studies which considered both preconception and pregnant couples, used uptake rates with 50% (preconception) & 90% (pregnant) [46], 50% (preconception) & 75% (pregnant) [47], and 20% (preconception) & 80% (pregnant) [17] respectively. The uptake rates of prenatal diagnosis if high-risk carrier/carriers identified were from 75% to 100% (Mean: 86%, Median: 85%).

Only six studies [17,32,40,44,52,57] reported test sensitivity and specificity for screening and prenatal diagnosis in full ranging from 90% to 100%, and other studies reported these values partially. However, one of the studies which examined the cost-effectiveness of CF screening for multiple ethnic groups reported that the test sensitivities of screening varied based on ethnicity, specifically, 90% for Whites, 75% for Black, 30% for Asians, and 57% for Hispanics [45].

Studies published before 2012 (n=20, 87%) did not take into account alternative reproductive options in their models, including in vitro fertilization (IVF) with pre-implantation genetic testing (PGT), adoption and gamete/embryo donation, after releasing positive screening/prenatal diagnosis results for preconception couples and for pregnant couples' subsequent pregnancies. The option of no reproduction in the future was considered in six studies [17,32,46-48,54], with the probability of such an event ranging from 15% to 25%. None of the selected studies adopted the probability that termination of pregnancy would occur prior to prenatal diagnosis.

The causes of miscarriage were roughly divided into two categories: prenatal-diagnosis associated and non-prenatal-diagnosis associated. Fourteen studies (61%) [17,39,40,43,46-49,52-54,56-58] included the rate of prenatal-diagnosis associated abortion (pregnancy loss as an adverse event following the procedure) in their analysis by using chorionic villus sampling (CVS) or amniocentesis, ranging from 0.29% to 1.5%, but the other nine (38%) [32,33,41,42,44,45,50,51,55] did not consider or explicitly state this value. Only four studies [43,46,47,54] applied the rate of non-prenatal-diagnosis associated abortion in their models, ranging from 1.55% to 3.5%.

Twenty studies (87%) explicitly reported the base year of costs in their analyses. Fewer than half of these 23 studies fully or partially considered costs of pre-screening in their models (n=11, 48%), including costs of individual information (such as leaflets), costs of mass information (such as mass media campaigns), and costs to organizations (such as education session for GP with genetic knowledge). For the costs of screening, prices ranged from US $34 to US $532 (2018 price) based on the variations of screening options, screened conditions and health systems. The costs of post-screening care included in these 23 studies were mainly with respect to costs of prenatal diagnosis (such as CVS) and costs of termination procedure, ranging from US $90 to US $2,491 and from US $310 to US $4,301 respectively (2018 price), according to the different healthcare systems in different counties. Eleven of the 20 studies with based year of cost reported lifetime costs of care per patient of less than one million, although the price range was broad, ranging from US $262,989 to US $7,838,036 (2018 price), depending on the conditions of interest in the studies.

3.4 Cost-effectiveness results

Ten (43%) [32,40,42,44,46,47,53,54,56,57] of these 23 selected studies reported more than one type of outcomes in their analyses, including monetary savings, number of screened women, number of carrier/carriers identified, number of affected pregnancies/fetuses identified, number of affected births averted, LYs gained, as well as QALYs (**Table 1**). The majority of the 23 studies applied lifetime as the time horizon in their analyses (**Table S1**). Seven of the selected studies (30%) [32,41-43,46,54,57] draw cost-effectiveness conclusions by comparisons between different strategies and scenarios of screening options in their analyses. Only four studies (17%) explicitly applied incremental cost-effectiveness ratio (ICER) threshold as a benchmark to make conclusions, including one with cost per life-year gained (US $50,000; 2018 price) [33] and three with cost per QALY [44,53,56].

The three studies using QALYs as their outcome measures [44,53,56] were all conducted in the US for single conditions (CF, FXS and SMA respectively). The study for CF [44] applied familial QALYs including both children and their parents' QALYs, whereas only maternal QALY was considered in the FXS [53] and SMA [56] studies. As a result, these studies made three different cost-effectiveness conclusions involving inconclusive [44], cost-effective [53] and not cost-effective [56] conclusions. The inconclusive study did not assign a threshold and their result was US $12,504 per QALY (2018 price). The study with a cost-effective result reported US $19,345 per QALY (2018 price) using US $100,000 per QALY as their threshold, whereas the study that concluded that the screening was not cost effective applied a range from US $50,000 to US $100,000 per QALY as their threshold,

but their result was far out of this range (US \$5.7 million, 2018) (**Table S3** in the supplemental materials).

3.5 Quality assessment of the included studies

The quality of all the selected studies was appraised using the CHEERS checklist (**Table S4** in the supplemental materials). The range of the scores was from 57% to 96% (Mean 82%; Median 83%). The studies published in the most recent decade (from 2010 to 2019) showed higher overall scores (Mean 95%; Median 96%) compared to the studies in earlier decades (Mean 75% and Median 76% from 2000 to 2009; Mean 78% and Median 78% from 1990 to 1999).

4. Conclusion

This review provides a comprehensive overview of recently published economic evaluations in RCS, presenting the first systematic review in this area considering multiple conditions among preconception and pregnant couples. Although examining single condition accounted for the majority of the published studies, assessing multiple conditions in one economic evaluation raised more concern recently because of the availability of advanced technologies. Cost-effectiveness conclusions varied largely because the studies used various clinical pathways/strategies and screened conditions when implementing carrier screening program. With the rapid advancement of medical technology in genetics, further research is required to establish cost-effectiveness of carrier screening programs for multiple conditions.

5. Expert opinion

For constructing economic models, a consensus clinical pathway of healthcare interventions is critical, which determines the structure of the model, as well as the choices of model inputs. Through our review, few studies fully considered the consequences that the high-risk couples will face. For preconception couples, they need to make choices among IVF with PGT, adoption, gamete/embryo donation, no reproduction, or natural pregnancy with or without prenatal diagnosis. For pregnant couples, most studies considered the termination of affected pregnancies, but did not take into account reproductive planning for subsequent pregnancies as an identified high-risk preconception couple. In addition, which items should be included in the process of pre-screening and post-screening is highly important for measuring costs. However, the selection of these

items was inconsistent between studies. For example, only a few studies considered pre-counselling in their models, which is particularly important to make couples fully informed before screening and is often recommended [59]. Last but not least, screening options can also impact the development of clinical pathways. For example, some studies examined cost-effectiveness compared between simultaneous (i.e. screening as couple unit) and sequential screening strategies (i.e. screening the female partner first, and only screening the male partner if the female is found to be carrier for an AR condition), which would influence the model structure and inputs. Therefore, a validated and practical clinical pathway is essential for implementing RCS, which can benefit clinical practice and economic research.

According to our review, many studies explicitly reported that their conclusions were highly sensitive to the estimated cost of genetic screening. In fact, with technological advancements, the cost of genetic screening has declined and may keep declining making it more affordable and accessible [16], although the introduction of large gene panels may lead to temporarily higher costs (but also a higher proportion of at-risk couples identified). It is suggested that using high-throughput technologies might be more cost-effective as they could identify multiple genetic disorders and variants in one single screening platform [56]. Indeed, researchers in recent years have been conducting economic evaluations of single point of screening for multiple conditions [32,33]. However, there is no consensus about which conditions should be included in the screening panel, and the systematic evidence-based selection of conditions remains an area of ongoing research. Consequently, economic

evaluations assessing screening for multiple conditions, and a systematic and evidence-based framework of condition selection are encouraged.

CUA is regarded as the gold-standard methodology in economic evaluations [17], because its outcome measure considers the individuals' quality of life, rather than monetary values. It also allows the comparison not only between different interventions for one specific disease, but also between different diseases by using QALY as the common unit to measure outcome [25]. However, only three studies applying CUA were identified within our review [44,53,56], and the approaches used in these CUA studies were not consistent. The CF cost-utility study [44] used time-trade-off methods by asking questions of teenage CF children and of parents of younger CF children as proxies, as well as parents' own quality of life related to having a child with CF. The preferences and utilities in the FXS study were obtained from one published literature review of Down syndrome [53]. The SMA study combined previously published data for SMA and Down syndrome [56]. On the other hand, twenty studies did not apply CUA in their analyses and the most common reason was because data were limited or not available. Furthermore, one study argued that since a healthy fetus in the subsequent pregnancy could not be guaranteed, it might not feasible to compare the quality of life between affected and healthy children [17]. Measuring maternal and/or paternal health related quality of life utility values appears more plausible than measuring children's, but these values may significantly vary depending on what condition the child is affected with.

One of the important factors that previously published reviews have not taken into account is the effect of subsequent pregnancy on cost-effectiveness conclusions [17]. In the three studies with reported ICER threshold, only one study's conclusion was that screening was not cost-effective, which did not include subsequent pregnancies in the analysis. The other two studies considered subsequent pregnancies and both of them make cost-effective conclusions. According to the 2016 census, for families with children in Australia, the number of children per woman was 1.8 on average [60]. Hence, it is appropriate to consider the subsequent pregnancy in the economic evaluation of carrier screening program. However, the average number of children within a family varies between countries, associated with the impacts of culture, religion, legal considerations and/or women's educational status.

Even though the mean and median values of the quality of all the selected studies were relatively high (Mean: 82%; Median: 83%), some assumptions seem to be implausible and ambiguous in these studies. For example, the termination rate of an affected pregnancy in some studies was assumed to be 100% [43,45,56], which may not be accurate due to the impacts of culture, religion or government policies in some places. Moreover, when data for AR and XL conditions were unavailable, some researchers used data from other conditions such as breast cancer [46] and Down syndrome [47,49]. Additionally, the outcome measures in the selected studies were various, implying the complexity of economic evaluations in this field [31], such as the challenges and difficulties in data collection of utilities and psychological impacts.

It is noteworthy, as a limitation of this review, that there were no studies from developing nations. Also, we did not compare the results directly across all interventions/screening options, since there were considerable inconsistencies and differences in many aspects of these studies such as the perspectives and methodologies.

This review presents the first systematic review of economic evaluations in RCS with multiple conditions. It also contributes a series of evidence-based recommendations for implementing RCS from a health economic point of view: 1) conducting a validated and practical clinical pathway of RCS is essential, which economic evaluations are based on; 2) contemporaneous economic evaluations assessing multiple genetic conditions are encouraged given the rapidly changing landscape of sequencing technology; 3) establishing systematic and evidence-based frameworks for condition selection is required; 4) developing more reliable instruments and approaches to measure QALY in the field of genetics would be beneficial; 5) subsequent pregnancy choices should be considered in future economic evaluation studies for RCS.

Declarations of Interests

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer Disclosures
Peer reviewers on this manuscript have no relevant financial relationships or otherwise to disclose.

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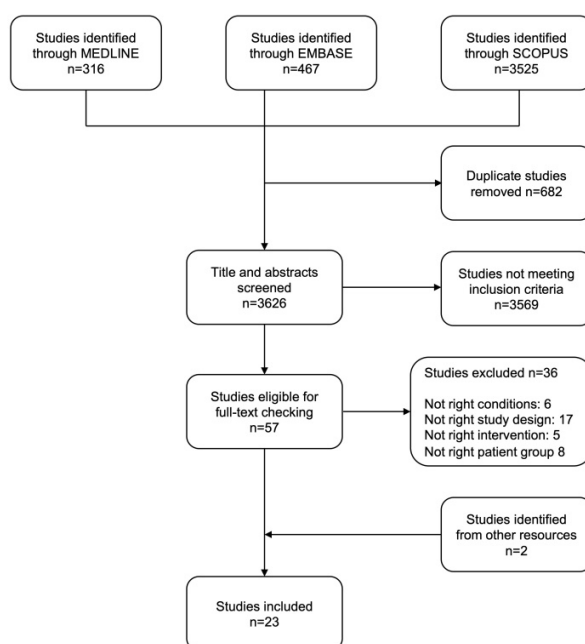
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Titles and Legends to Figures

Fig. 1 Preferred Reporting System for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram of the different phases of the systematic review


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┌─────────────────┐   ┌─────────────────┐   ┌─────────────────┐
│Studies identified│   │Studies identified│   │Studies identified│
│through MEDLINE  │   │through EMBASE   │   │through SCOPUS   │
│n=316            │   │n=467            │   │n=3525           │
└─────────────────┘   └─────────────────┘   └─────────────────┘

                                           ┌─────────────────┐
                                           │Duplicate studies │
                                           │removed n=682     │
                                           └─────────────────┘

          ┌─────────────────┐              ┌─────────────────┐
          │Title and abstracts│            │Studies not meeting│
          │screened          │──────────→ │inclusion criteria │
          │n=3626            │             │n=3569            │
          └─────────────────┘              └─────────────────┘

          ┌─────────────────┐   ┌──────────────────────────┐
          │Studies eligible for│  │Studies excluded n=36      │
          │full-text checking  │→ │Not right conditions: 6    │
          │n=57              │   │Not right study design: 17 │
          └─────────────────┘   │Not right intervention: 5  │
                                 │Not right patient group 8  │
                                 └──────────────────────────┘

                                 ┌─────────────────┐
                                 │Studies identified │
                                 │from other resources│
                                 │n=2              │
                                 └─────────────────┘

          ┌─────────────────┐
          │Studies included  │
          │n=23             │
          └─────────────────┘
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Fig. 2 The categories of the intervention/screening options used in the selected studies (totally 23) distributed by publication years from 1990 to 2019
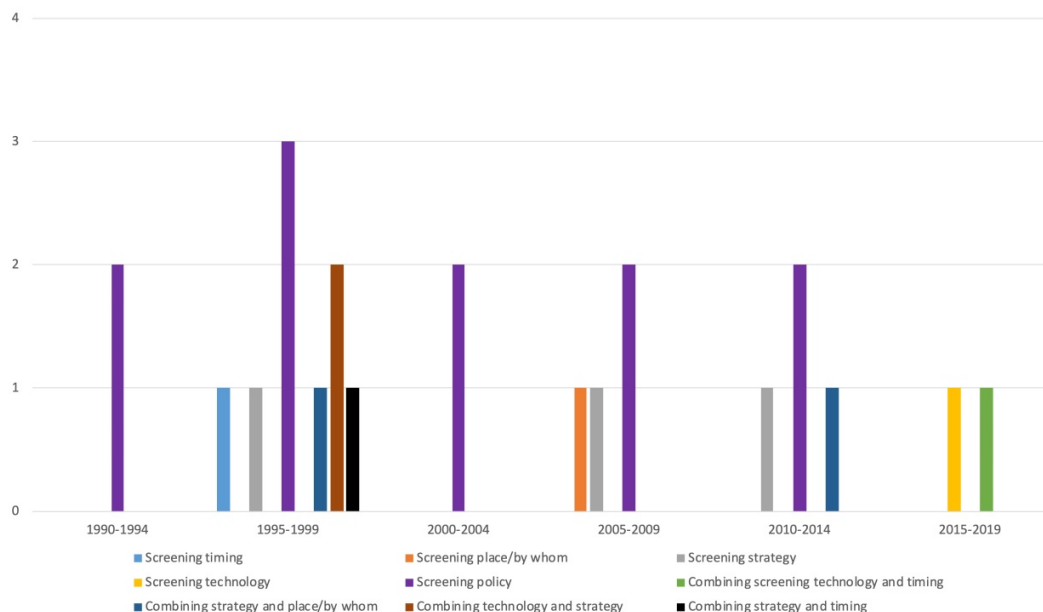
Fig. 3 A clinical pathway of reproductive carrier screening (RCS) for both preconception and pregnant couples

The left part of the figure: the proposed clinical process for couples who undertake RCS; the middle of the figure: the associated probabilities alongside the clinical process, which can be collected and applied in the economic model; the right part of the figure: the associated cost data alongside the clinical, which can be collected and applied in the economic model.

Couples → Screening acceptance → Low-risk carriers / High-risk carriers → Preconception / Pregnant

Preconception:
- IVF with PGT
- Gamete/embryo Donation
- Adoption
- No reproduction

Natural pregnancy

Prenatal diagnosis

No testing during pregnancy

Unaffected pregnancy — Affected, pregnancy continued — Affected, pregnancy terminated

Unaffected birth — Affected birth

Probability of screening acceptance — Cost of pre-screening

Test sensitivity & specificity (screening) — Cost of screening

Probability of reproductive choices

Probability of prenatal diagnosis acceptance — Cost of post-screening

Test sensitivity & specificity (prenatal diagnosis)

Cost of care for affected people

ACCEPTED

Table 1   Characteristics of the selected economic evaluations in RCS (n, %[a])

Characteristic	Studies (n=23)
Year of publication	
1990-1999	11 (48%)
2000-2009	6 (26%)
2010-2019	6 (26%)
Study country	
Australia	3 (13%)
Denmark	1 (4%)
Israel	1 (4%)
Netherlands	4 (17%)
United Kingdom	3 (13%)
United States	11 (48%)
Type of recessive condition	
Autosomal	18 (78%)
X-linked	4 (17%)
Both	1 (4%)
Recessive condition	
Cystic Fibrosis	15 (65%)

Fragile X Syndrome	4 (17%)
Spinal Muscular Atrophy	1 (4%)
Sickle Cell disease & Thalassemia	1 (4%)
Multiple conditions	2 (9%)

Methodology

CBA	8 (35%)
CEA	9 (39%)
CBA + CEA	3 (13%)
CBA + CUA	1 (4%)
CEA + CUA	1 (4%)
CBA + CEA + CUA	1 (4%)

Type of the population group

Preconception	3 (13%)
Pregnancy	14 (61%)
Both	5 (22%)
Not specifically record	1 (4%)

Type of intervention/screening option

Timing	1 (4%)
Place/by whom	1 (4%)

Strategy	3 (13%)
Technology	1 (4%)
Policy	11 (48%)
Combined	6 (26%)

Type of outcome[b]

Savings	11 (48%)
Number of screened women	1 (4%)
Number of carrier/carriers identified	5 (22%)
Number of affected pregnancies/foetuses identified	5 (22%)
Number of affected birth averted	8 (35%)
LYs gained	2 (9%)
QALY	3 (13%)

Study perspective

Private health insurer	1 (4%)
Health sector	8 (35%)
Third-party payer	2 (9%)
Societal	9 (39%)
Multiple	3 (13%)

Discount rate

3%	7 (30%)
3.5%	1 (4%)
4%	1 (4%)
5%	6 (26%)
Not reported	8 (35%)
Well-reported of	
Time horizon	23 (100%)
Intervention	23 (100%)
Comparator	16 (70%)
Sensitivity analysis used	22 (96%)

[a]All the percentages were rounded up to integers.

[b]Ten studies (43%) adopted multiple types of outcome measures.

CBA: cost-benefit analysis

CEA: cost-effectiveness analysis

CUA: cost-utility analysis

LYs gained: Life years gained

QALY: quality-adjusted life year

Table 2   Example for different interventions/screening options

Intervention/screening option	Example
Screening timing	e.g. Before or during pregnancy
Screening place/by whom	e.g. General practice (GP)
Screening strategy	e.g. Screening the couple simultaneously or sequentially
Screening technology	e.g. Next-generation sequencing
Screening policy	e.g. A population-wide screening program
Combined screening options	e.g. Preconception sequential screening