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Interest in expanded carrier screening among individuals and couples in the general population: systematic review of the literature

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BACKGROUND: Through carrier screening, prospective parents can acquire information about whether they have an increased risk of conceiving a child affected with an autosomal recessive or X-linked condition. Within the last decade, advances in genomic technologies have facilitated a shift from condition-directed carrier screening to expanded carrier screening (ECS). Following the introduction of ECS, several studies have been performed to gauge the interest in this new technology among individuals and couples in the general population.

OBJECTIVE AND RATIONALE: The aim of this systematic review was to synthesize evidence from empirical studies that assess the interest in ECS among individuals and couples in the general population. As the availability and accessibility of ECS grow, more couples who are *a priori* not at risk based on their personal or family history will be presented with the choice to accept or decline such an offer. Their attitudes and

beliefs, as well as the perceived usefulness of this screening modality, will likely determine whether ECS is to become a widespread reproductive genetic test.

SEARCH METHODS: Four databases (Pubmed, Web of Science, CINAHL, Cochrane Library) were systematically searched to identify English language studies performed between January 2009 and January 2019 using the following search terms: carrier screening, carrier testing, attitudes, intention, interest, views, opinions, perspectives and uptake. Studies were eligible for inclusion if they reported on intentions to undergo a (hypothetical) ECS test, uptake of an actual ECS offer or both. Two researchers performed a multistep selection process independently for validation purposes.

OUTCOMES: Twelve empirical studies performed between 2015 and 2019 were included for analysis. The studies originated from the USA ($n = 6$), the Netherlands ($n = 3$), Belgium ($n = 1$), Sweden ($n = 1$) and Australia ($n = 1$). The sample size of the studies varied from 80 to 1669. In the included studies, 32%–76% of respondents were interested in a (hypothetical) ECS test, while uptake rates for actual ECS offers ranged from 8% to 50%. The highest overall uptake was observed when ECS was offered to pregnant women (50%). By contrast, studies focusing on the preconception population reported lower overall uptake rates (8–34%) with the exception of one study where women were counseled preconception in preparation for IVF (68.7%).

WIDER IMPLICATIONS: Our findings suggest that there may be discrepancies between prospective parents' reported intentions to undergo ECS and their actual uptake, particularly during the preconception period. As ECS is a new and relatively unknown test for most future parents, the awareness and comprehension within the general population could be rather limited. Adequate pre- and post-test counseling services should be made available to couples offered ECS to ensure informed reproductive decision-making, together with guidelines for primary health care professionals. Due to restricted nature of the samples and methods of the underlying primary studies, some of the reported results might not be transferable to a broader population. More research is needed to see if the observed trends also apply to a broader and more diverse population.

Key words: expanded carrier screening / reproductive genetics / attitudes / intention / interest / uptake

Introduction

Through carrier screening, prospective parents can acquire information about whether they have an increased risk of conceiving a child affected with a recessive genetic condition. When both partners are identified as carriers of the same autosomal recessive disorder, they have a 25% chance of having an affected child in each pregnancy. When the mother is a carrier of an X-linked recessive disorder, there is a 50% chance that the couple's male offspring will be affected. Approximately, 1–2% of couples in the general population have an increased risk of conceiving a child affected with an autosomal recessive or X-linked condition ('carrier couples') (Ropers 2012). Because carriers are typically healthy and lack family history for genetic conditions, they are usually unaware of their reproductive risk until their child is diagnosed with a genetic disorder (Henneman *et al.*, 2016).

Carrier screening for recessive conditions was first made available in the early 1970s. Traditionally, genetic carrier screening has focused on recessive disorders with significant morbidity and reduced life expectancy in specific ethnic communities. Examples are carrier screening for Tay–Sachs disease affecting the Ashkenazi Jewish population and beta-thalassaemia in several at-risk populations in the Mediterranean area (Kaback 2000). Recent advances in genomic technologies are facilitating a shift from condition-directed carrier screening to expanded carrier screening (ECS). ECS offers carrier screening for a large number of recessive conditions in the same panel, regardless of ancestry and geographic origin of users (Edwards *et al.*, 2015). The development of the first commercial ECS test, which screened for 108 recessive conditions, was reported in 2010 (Lazarin *et al.*, 2013). This introduction was followed by various (commercial) providers that made ECS tests available to prospective parents (Chokoshvili *et al.*, 2018).

In most Western countries, there is a consensus that carrier screening should strengthen reproductive autonomy and enable informed reproductive choices based on the personal values and preferences of a couple (Henneman *et al.*, 2016). When 'carrier couples' want to act upon positive screening results they can opt for prenatal diagnosis, IVF/ICSI combined with preimplantation genetic testing (PGT), gamete donation, adoption or refraining from having children together (Henneman *et al.*, 2016). In contrast, carrier couples who are identified during pregnancy only have the option to undergo prenatal diagnosis or not. If the fetus is found to be affected, the couple has the option to prepare for a child with a particular recessive condition or to terminate the pregnancy.

Several medical professional organizations have published recommendations regarding ECS within the last few years. In 2015, the American College of Medical Genetics and Genomics (ACMG), the American College of Obstetricians and Gynecologists (ACOG), the National Society of Genetic Counselors, the Perinatal Quality Foundation and the Society for Maternal-Fetal Medicine issued a joint statement on ECS, which stated that 'women of reproductive age should ideally be offered carrier screening before conception' (Edwards *et al.*, 2015). Following this statement, ACOG released a Committee Opinion in 2017 stating that 'health care providers should establish approaches where carrier screening is consistently offered to and discussed with each patient, if possible before pregnancy' (ACOG 2017). In 2016, the European Society of Human Genetics also issued recommendations regarding the responsible implementation of ECS. These recommendations emphasized 'that ECS should preferably be offered before pregnancy' (Henneman *et al.*, 2016). Even though existing professional guidelines emphasize that ECS should ideally be offered before conception, practical limitations could be encountered when trying to reach for this specific group. Experience shows that pregnant women, in

comparison to couples planning a pregnancy, are more easily reachable through health care providers who guide them through their pregnancy (Henneman *et al.*, 2016).

Earlier studies focusing on condition-specific carrier screening (e.g. cystic fibrosis (CF) screening) showed overall positive attitudes toward carrier screening among individuals in the general population. In these studies, highly educated Caucasian women who had no children and were planning future pregnancies were more likely to accept an offer of screening (Ioannou *et al.*, 2014b). Even though participants believed that the best time to have CF carrier screening would be before pregnancy, preconception screening was associated with a lower uptake than prenatal screening (Clayton *et al.*, 1996; Henneman *et al.*, 2003; Henneman *et al.*, 2016). According to Poppelaars *et al.* (2003), this might be due to a lack of interest in carrier screening during the preconception period, an absence of established preconception healthcare services through which to offer screening and a high number of unplanned pregnancies (Poppelaars *et al.*, 2003). Conversely, pregnancy has been identified as a strong motivating factor for undergoing CF carrier screening, suggesting that CF carrier screening may be perceived as more relevant during pregnancy by expectant parents (Poppelaars *et al.*, 2003; Ioannou *et al.*, 2014b).

As the availability and accessibility of ECS grow, more couples will be presented with the choice to accept or decline such an offer. Their attitudes and beliefs, as well as the perceived usefulness of this screening modality will likely determine whether ECS is to become a widespread reproductive genetic test. It is possible that similar factors are influencing the decision-making process of prospective parents regarding ECS in comparison to single gene carrier screening. It may be assumed that carrier couples who do not feel comfortable with the available reproductive options (e.g. IVF/ICSI combined with PGT) will also not be interested in ECS. However, it is also possible that the expansion of panels may increase the perceived benefits of screening (Henneman *et al.*, 2016). More insights are needed to understand how individuals and couples process information when ECS is offered to them and which factors affect individuals' decisions to undergo or forgo ECS. Following the introduction of ECS, several studies have been performed to gauge the interest in ECS among the general population. The aim of this systematic review is to synthesize evidence from empirical studies that assess the interest in/uptake rates for ECS among individuals and couples in the general population and to identify factors associated with the decision to accept or decline ECS.

Methods

Design and search strategy

We used a comprehensive search approach to identify empirical studies that focused on the assessment of the intention to undergo a (hypothetical) carrier screening test, uptake of an actual carrier screening offer, or both. The review process consisted of three main steps. First, we systematically searched for relevant publications in four online databases (Pubmed, Web of Science, CINAHL, Cochrane Library) that were published from January 2009 to January 2019. Because panethnic screening or ECS was introduced to the market in 2009, studies published prior to 2009 were not included in this review (Srinivasan *et al.*, 2010; Lazarin *et al.*, 2013). In order to identify relevant studies, the following search string was used: *'carrier' AND ('testing'[tw] OR 'screening' [tw]) AND (attitude [tw] OR intention [tw] OR interest [tw] OR views [tw] OR opinions [tw] OR perspectives [tw] OR uptake [tw])*. Second, we consulted references of the relevant papers identified through the systematic search in order to find any additional publications warranting inclusion in the review (i.e. snowball method). Finally, we carried out a 'related search' strategy (Google Scholar) to track for any other potentially relevant studies based on the studies identified through the systematic search of the four online databases. Our review followed PRISMA guidelines for systematic reviews of the medical literature (Liberati *et al.*, 2009).

Inclusion and exclusion criteria

Studies were included in the review if they met all of the following criteria: quantitative studies assessing the intention to take a (hypothetical) carrier screening test and/or an actual uptake of a carrier screening offer; the study population was *a priori* not at risk based on their personal or family history; and studies published between January 2009 and January 2019.

Studies/articles were excluded if they met any of the following criteria: studies assessing the interest in or uptake of genetic tests aimed at obtaining non-reproductive medical information (e.g. predictive genetic testing/predisposition as in breast cancer or diagnostic testing in patients with disease symptoms); studies focused on genetic tests targeting dominant genetic disorders; studies assessing the interest in or uptake of a carrier screening test within specific communities (e.g. Ashkenazi Jewish Community); publications other than original research articles (e.g. reviews or opinion articles); publications in a language other than English. When the results of a single research project were reported in multiple publications, we only included one research article for this review.

Search outcomes

Records identified through searching the four databases were subsequently aggregated into a single library, containing 1554 unique records (excluding duplicates). Initially, all 1554 items were screened based on their title, and the records deemed potentially relevant by at least one of the two researchers were retained. Subsequently, 209 abstracts were read by both researchers. As a final step, 23 full-text articles were read by both researchers after the exclusion of non-relevant abstracts. The review of the collected literature was performed by two researchers (E.V.S. and D.C.) who worked independently and continually discussed their findings to identify and resolve any differences. The decision on whether to retain an abstract or article was made based on mutual agreement.

Our search led to the identification of nine studies that were included in the review. We also included two additional studies (Higgins *et al.*, 2015; Schuurmans *et al.*, 2018) identified through snowball sampling, as well as one study that was published days after performing the search to identify relevant empirical studies (Larsen *et al.*, 2019). These 12 studies have either surveyed respondents on their willingness to undergo ECS, offered an actual ECS test to prospective parents or retrospectively reviewed medical records of women who had preconception/prenatal ECS. For each identified study our 'relevant search' strategy displayed 100 related articles. No new studies were identified throughout this final step. Figure 1 graphically summarizes the literature search process.

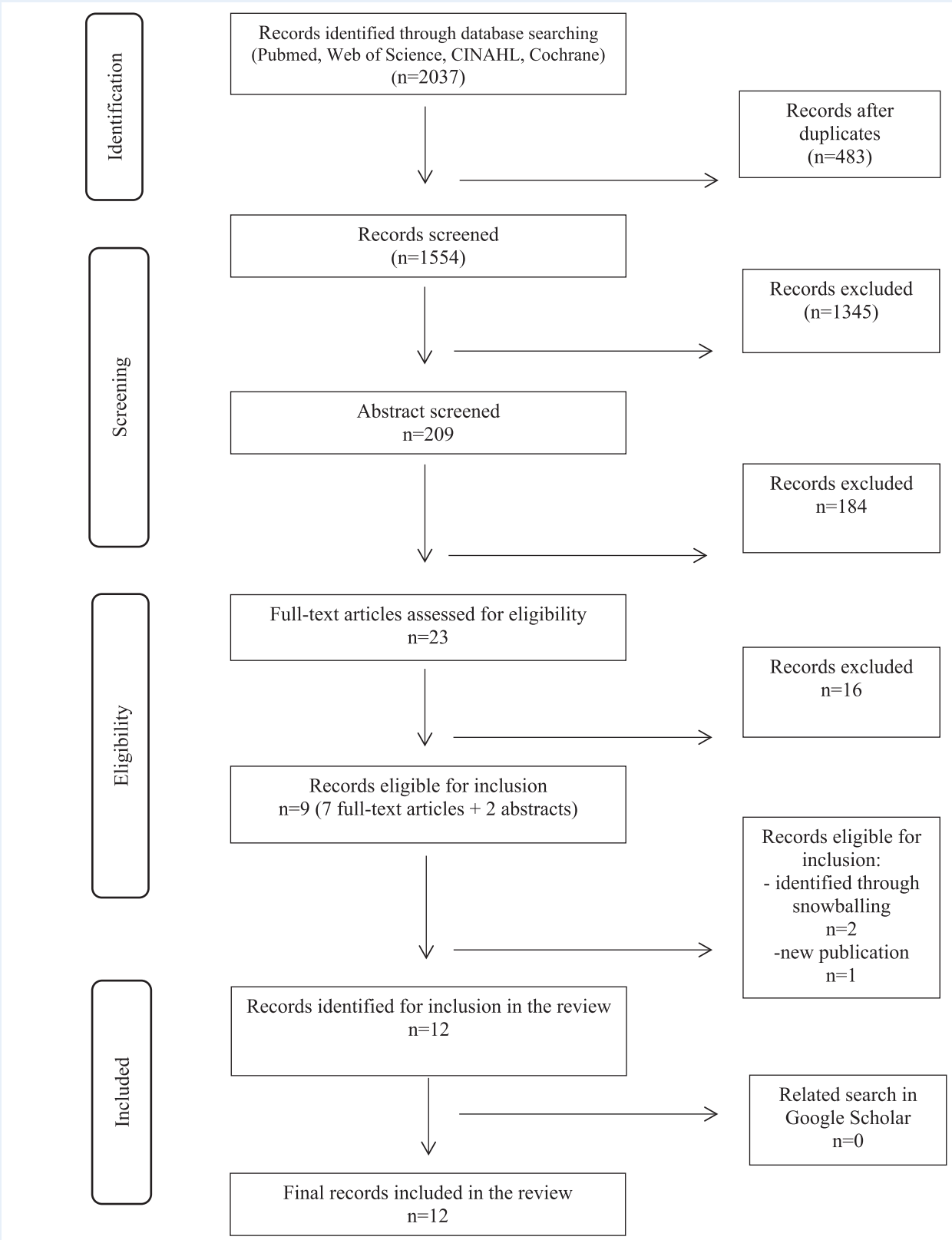

Figure 1 **Identification and selection of articles in a systematic review of the interest in ECS among individuals and couples in the general population.**

The flowchart is organized according to the PRISMA guideline outlined in Liberati *et al.*, (2009).

Quality appraisal

We performed an indicative quality appraisal of each of the included articles using the tool developed by Hawker *et al.* (2002). By using this system, we were able to indicate the methodological rigor of the included study based on the information provided by the authors of the included studies. Articles were not excluded from our systematic review based on their methodological quality. The quality appraisal was performed independently by two researchers. In case of disagreement, the specific item was discussed until mutual agreement.

Results

Quality appraisal

The results of the quality appraisal are summarized in Table I. Almost all studies included in this review had well-structured abstracts with a clear description of the study and a clear title. In addition, the full-text articles included in this review provided a concise literature review and a clear statement aim of the study. The methodology of the included studies was clearly explained and appropriate to the study aim, including an overview off the data collection tools and methods. Most of the studies provided a fairly detailed description of the data analysis performed, but only one study clearly outlined the hypothesis behind the statistical test selection. The results section of the included articles reported results directly related to the aims and were logical and easy to understand. Findings presented were supported with sufficient data. All studies gained necessary ethical approval but only a few studies addressed ethical issues in more detail. Most authors gave a clear description of the sampling strategy used to address the aims. However, the sample size was not always justified and specific groups were often targeted using convenience sampling. As a result, the transferability and generalizability of some of the reported results are questionable. Most of the studies provided implications for policy and practice and some suggested ideas for further research. However, the implications and usefulness of the reported results of some studies might not be transferable to a broader population. The authors of these specific papers acknowledge this limitation and underline the importance to expand upon the reported findings by increasing sample size and population diversity.

Study characteristics

A detailed overview of the underlying study methods of the primary empirical studies included in this systematic review is presented in Table II. Variables for which data were sought include the country where the study took place, the type of record, the study aim, the study duration, the study population (including sample size), inclusion/exclusion criteria, recruitment strategy, data collection, data analysis, ethical considerations and costs for participants.

The publication range of the 12 studies included in this systematic review dates from 2015 to 2019. The articles originate from five different countries: the USA ($n = 6$), the Netherlands ($n = 3$), Belgium ($n = 1$), Sweden ($n = 1$) and Australia ($n = 1$). The sample size of the studies varied greatly from 80 to 1669. The majority of the

Table I Quality appraisal of studies included in this systematic review of the interest in ECS among individuals and couples in the general population.

Study	Abstract and Title	Introduction and Aims	Method and Data	Sampling	Data analysis	Ethics and bias	Results	Transferability and Generalizability	Implication and usefulness	Overall Assessment
Higgins *et al.* 2015	Good	Good	Good	Fair	Fair	Poor	Fair	Fair	Fair	High
Plantinga *et al.* 2016	Good	Good	Good	Good	Fair	Fair	Good	Fair	Good	High
Ragnar *et al.* 2016	Good	Good	Good	Good	Good	Good	Good	Fair	Good	High
Chokoshvili *et al.* 2017	Good	Good	Good	Fair	Fair	Poor	Good	Fair	Fair	High
Briggs *et al.* 2017*	Good	NA	NA	NA	NA	NA	NA	NA	NA	NA
Gilmore *et al.* 2017	Good	Good	Good	Poor	Fair	Fair	Good	Poor	Good	High
Ong *et al.* 2018	Good	Good	Good	Fair	Good	Fair	Good	Fair	Fair	High
Propst *et al.* 2018	Good	Good	Good	Poor	Fair	Fair	Good	Poor	Good	High
Spencer *et al.* 2018	Fair	Good	Good	Fair	Fair	Good	Good	Poor	Good	High
Schuurmans *et al.* 2018*	Good	NA	NA	NA	NA	NA	NA	NA	NA	NA
Nijmeijer *et al.* 2019	Good	Good	Good	Good	Fair	Fair	Good	Fair	Fair	High
Larsen *et al.* 2019	Good	Good	Good	Fair	Fair	Poor	Fair	Poor	Good	High

The quality appraisal was performed using the tool developed by Hawker *et al.* (2002). For each included study the following questions were scored: Did they provide a clear description of the study?; Was there a good background and clear statement of the aims of the research?; Is the method appropriate and clearly explained?; Was the sampling strategy appropriate to address the aims?; Was the description of the data analysis sufficiently rigorous?; Have ethical issues been addressed, and was necessary ethical approval gained?; Is there a clear statement of the findings?; Are the findings of this study transferable to a wider population?; How important are these findings to policy and practice?
*Conference abstracts: quality appraisal was only performed for the provided abstract.

Table II Overview of the underlying study methods of the primary empirical studies on ECS included in this systematic review.

Study (Country)	Type	Study aim	Study duration	Study Population	Inclusion criteria	Exclusion criteria	Recruitment	Data-collection	Data analysis	Ethical considerations	Costs for participants
Higgins *et al.* 2015 (USA)	Full-text article	To determine whether availability of a more comprehensive, affordable genetic screening tool increased the number of patients choosing to have preconception screening.	36 months (retrospective)	Patients evaluated for primary or secondary infertility. (n = 1669)	Evaluation for either primary or secondary infertility including both male and female factors (low or abnormal sperm counts, recurrent miscarriages, PCOS, ovarian dysfunction, uterine abnormalities, or female infertility of unknown origin).	Couples seeking genetic counseling or referred for genetic counseling who did not have complaints of infertility, family members seeking genetic screening when abnormalities where found on screening results.	Search of the electronic medical records at Sanford Health Fertility and Reproductive Medicine AND Counsyl Database	Retrospective medical record review	Descriptive analysis	Institutional review board approved study.	The maximum out-of-pocket cost for patients was $349 and decreased to $99 in May 2012.
Plantinga *et al.* 2016 (The Netherlands)	Full-text article	To investigate potential users' intentions to undertake preconception carrier screening and through which provider they would like to see it offered.	1 month	Men and women with a partner in the reproductive age. Sample was stratified according to gender, educational level and geographical region. (n = 504)	Individuals aged 18–40 years, having a partner, living in the Netherlands.	/	Online recruitment by a survey research sampling company.	Online Survey; Custom Developed Questionnaire	Descriptive analysis, Fisher's Exact tests	Ethical approval from the Medical Ethical Review Committee of the University Medical Center Groningen.	NA

(Continued)

Table II Continued.

Study (Country)	Type	Study aim	Study duration	Study Population	Inclusion criteria	Exclusion criteria	Recruitment	Data-collection	Data analysis	Ethical considerations	Costs for participants
Ragnar *et al.* 2016 (Sweden)	Full-text article	To investigate parents' interest and motives towards preconception genetic carrier screening (PCS) as well as factors associated with interest in PCS.	10 months	Pregnant women recruited at registration in the antenatal clinic. Study sample consists of parents couples who had responded to all questionnaires. (n = 777)	Pregnancy, registration in antenatal clinic.	/	Swedish Pregnancy Planning Study - longitudinal cohort study	Survey; One questionnaire in early pregnancy, one questionnaire around gestational week 34, one questionnaire 12 months post-partum, partner-questionnaire 12 months post-partum	Descriptive analysis, McNemer-Bowker's test, Binary Logistic Regression	Approval by the regional ethical review board in Uppsala (Sweden), voluntary participation, participants were informed that care given at the antenatal clinic was not related to study participation, informed consent was obtained from all participants.	NA
Chokoshvili *et al.* 2017 (Belgium)	Full-text article	To explore the views of the Belgian public on various topics surrounding genetics and genetic testing.	2 months	Visitors of the annual cartoon festival (convenience sampling). (n = 1182)	Aged 18 years or older (minors aged 16 years or older were also included, provided they were accompanied by an adult family member and actively expressed interest in participation), fluency in Dutch.	/	Cartoon festival	Survey; Custom developed questionnaire administered in person	Descriptive analysis, Mann-Whitney U Test, Kruskal-Wallis test	Ethical approval from the Social and Societal Ethics Committee of the University of Leuven.	NA

(Continued)

Table II Continued.

Study (Country)	Type	Study aim	Study duration	Study Population	Inclusion criteria	Exclusion criteria	Recruitment	Data-collection	Data analysis	Ethical considerations	Costs for participants
Briggs *et al.* 2017 (USA)	Abstract	To evaluate the awareness and attitudes among women regarding preconception carrier screening and factors that may influence decision-making in a family planning context.	/	Women who were pregnant, undergoing gynecologic care who were considering future fertility and infertility patients. (n = 521)	/	/	Academic University Practice	Survey; Questionnaire	Descriptive analysis	/	NA
Gilmore *et al.* 2017 (USA)	Full-text article	To evaluate reasons for declining preconception carrier screening.	/	Members of Kaiser Permanente Northwest (KPNW) (healthcare delivery system). (n = 240)	Current member of KPNW, not pregnant, stating to plan future pregnancies, previously completed PCS for CF through clinical care at KPNW.	Pregnant at the time of recruitment or consent visit, not access to email, a known cognitive impairment, not able to speak English, not aged 21–50 years.	Database KPNW healthcare delivery system	Telephone Survey; Custom developed questionnaire.	Descriptive analysis, Fisher's Exact tests, Multivariable logistic regression	Approval by the Kaiser Permanente Northwest Institutional Review Board. Verbal consent was obtained from all participants.	NA

(Continued)

Table II Continued.

Study (Country)	Type	Study aim	Study duration	Study Population	Inclusion criteria	Exclusion criteria	Recruitment	Data-collection	Data analysis	Ethical considerations	Costs for participants
Ong *et al.* 2018 (Australia)	Full-text article	To explore baseline levels of genetic knowledge and awareness regarding PCS in Western Australia prior to the implementation of any public health campaign without specifying what PCS means AND to investigate factors that might influence knowledge and attitudes to participation in any future PCS program implemented in Western Australia.	2 weeks	Individuals on four online panels of Western Australian residents. (n = 832)	Aged 18 years or older, residing in Western Australia.	/	Online recruitment by a market research agency	Online Survey; Custom developed questionnaire	Descriptive analysis, Chi-Square test of independence, multinomial logistic regression, ordinal logistic regression	Ethical approval from the Human Research Ethics Committee of the University of Western Australia.	NA
Propst *et al.* 2018 (USA)	Full-text article	To explore pregnant woman's perspectives to expanded carrier screening, including reasons for electing or declining and anxiety associated with tis decision-making.	4 months	Pregnant Women. (n = 80)	Female, pregnancy, able to read and speak English, aged 18 years or older, individuals who previously had ethnicity-based carrier screening.	Minors, not pregnant, not able to read or speak English, individuals who already had ECS.	Pregnant women undergoing prenatal genetic counseling prior to pursuing aneuploidy screening at Northwestern Medicine in Chicago	Survey; Custom developed questionnaire	Descriptive analysis, Mann-Whitney U Test, Chi-Square test of independence	Approval by the Northwestern University Institutional Review Board.	Up to $350 out-of-pocket if participant' insurance did not cover the test.

(Continued)

Table II Continued.

Study (Country)	Type	Study aim	Study duration	Study Population	Inclusion criteria	Exclusion criteria	Recruitment	Data-collection	Data analysis	Ethical considerations	Costs for participants
Spencer *et al.* 2018 (USA)	Full-text article	To better understand the opinions and attitudes of adopted individuals on the use of ECS in determining a patient's reproductive genetic risks.	8 weeks	Adult adoptees. (n = 124)	Aged 18 years or older, to have been adopted.	/	Distribution of study invitation through multiple non-profit organizations in the adoption community.	Online Survey; Custom developed questionnaire	Descriptive analysis, Chi-Square test of independence, Fisher' Exact test, Gamma Correlation Test, Binary Logistic Regression	Approval by the Northwestern University Institutional Review Board. Consent was implied once participants initiated the online survey.	NA
Schuurmans *et al.* 2018 (The Netherlands)	Abstract	To investigate short- and long-term psychological impact as well as uptake and feasibility of a GP-provided couple-based ECS test.	Longitudinal	Patients from GP-practices. (n = 190)	Female, having a male partner, planning children and not being pregnant.	/	GPs from nine practices invited female patients from their practice register.	Longitudinal survey study; Custom developed questionnaire	T-tests/non-parametric tests	/	Free of charge

(Continued)

Table II Continued.

Study (Country)	Type	Study aim	Study duration	Study Population	Inclusion criteria	Exclusion criteria	Recruitment	Data-collection	Data analysis	Ethical considerations	Costs for participants
Nijmeijer *et al.* 2019 (The Netherlands)	Full-text article	To assess public attitudes towards preconception ECS for autosomal recessive disorders in order to learn more about public acceptance and to address possible misconceptions.	12 months (retrospective)	A stratified sample of Dutch individuals. (n = 781)	Aged 18–45 years.	/	Online recruitment by a market research agency.	Online Survey; Custom developed questionnaire	Descriptive analysis, Chi-Square test of independence, independent sample t-test, multivariate logistic regression analysis	Informed consent was obtained from participants prior to completing the online questionnaire. The study was approved by the Medical Ethics Committee of Amsterdam UMC.	NA
Larsen *et al.* 2019 (USA)	Full-text article	To identify factors associated with individual decisions to proceed with ECS after genetic counseling.	1 month	Women who had a prenatal or preconception genetic counseling encounter with genetic counselors for various indications. (n = 483)	Individualized genetic counseling by board-certified genetic counselors. Being offered ECS.	/	Database with 500 medical records from women who had a prenatal or preconception genetic counseling encounter at a genetic clinic counseling service in an urban private hospital-based outpatient clinic.	Retrospective medical record review.	Descriptive analysis, Chi-Square test of independence, Two-tailed t-tests.	Approval by institutional review board for human subjects research.	NA

ECS: expanded carrier screening, CF: cystic fibrosis, GP: general practitioner

Table III Main findings of studies exploring the interest in and uptake of ECS.

Study	Composition of test panel	Study population	Reported measures relevant to ECS	Main findings	Participants characteristics
Higgins et al. 2015	106 genetic conditions	Couples undergoing fertility evaluation at Sanford Health Fertility and Reproductive Medicine were offered a commercial ECS test between 2010 and 2013. (n = 1669)	Uptake of ECS	134 couples (8%) underwent screening for either one or both partners (48.5% of the couples screened both partners and 44% screened only the female partner). The uptake increased from 3.3% to 17.5% following the decrease in out-of-pocket cost of screening from $350 to $99.	97% non-Hispanic Caucasian (94% of the total cohort offered ECS were non-Hispanic Caucasian); 31% of individuals were identified as carriers of at least one serious genetic disease.
Plantinga et al. 2016	Hypothetical test panel for 50 diseases	Dutch residents aged 18–40 years with a partner. (n = 504)	Intention to participate in preconception ECS	Over one-third (34%) of the respondents indicated they would take the test if it were offered, 15% reported they were unlikely to take the test, and 51% were undecided.	72% of respondents were female; mean age was 29 (SD 6.19); 65% of respondents were not religious; 34% had a high education level; 70% of respondents expressed the desire to have children with their current partner.
Ragnar et al. 2016	Hypothetical generic test panel	Couples enrolled in the Swedish Pregnancy Planning study (SWEPP). (n = 777)	Intention to participate in preconception ECS	Approximately one-third (30% of women; 33.6% of men) of the respondents indicated interest in screening; 25.5% of women and 28.2% of men were not interested, while 44.5% of women and 38.2% of men were uncertain.	Mean age was 29.8 years (SD 4.6) for woman and 35.3 years (SD 5.6) for men; 59.8% of women had a university/college degree compared to 44% of men; 78.2% of women already had children; 23% of women had a previous miscarriage; approximately 80% of pregnancies were planned; 59.6% of respondents had experiences of prenatal diagnostics; 54.6% of women had a future child wish compared to 43.6% of men.
Chokoshvili et al. 2017	Hypothetical generic test panel	Visitors of the annual Cartoon festival. (n = 1182)	Intention to participate in preconception ECS	54% of the respondents showed intention to participate in PCS for recessive disorders.	52.5% of respondents were female; mean age was 48.5 years (SD 16.8); 31.6% described themselves as (somewhat) actively religious; 34.8% had an academic degree.
Briggs et al. 2017	Hypothetical generic test panel	Pregnant women, women undergoing gynaecologic care who were considering future fertility and infertility patients. (n = 521)	Intention to participate in genetic carrier screening	51% of the respondents reported no desire for testing.	/
Gilmore et al. 2017	750 autosomal recessive, X-linked and mitochondrial conditions +100 medically actionable secondary findings	Non-pregnant women (aged 21–50) who had declined to undergo a preconception ECS offered free of charge in the research setting. (n = 240)	Uptake of ECS; Reasons for declining testing	In total, 816 women were offered preconception ECS, 540 (66%) of whom declined the offer. Among the decliners, 240 (44%) agreed to participate in the telephone interview study.	76% of respondents were non-Hispanic white; 77% had a Bachelor's degree or higher; 82% of respondents were 30 years or older; 38% of women had children.

(Continued)

Table III Continued.

Study	Composition of test panel	Study population	Reported measures relevant to ECS	Main findings	Participants characteristics
Ong *et al.* 2018	Hypothetical generic test panel	Residents of Western Australia aged 18 years or older. (n = 832)	Intention to participate in preconception ECS	Overall, 68% (n = 562) of the respondents indicated interest in ECS, although the intention to undergo ECS varied (61%–92%) depending on the nature of disorders to be included in the test. Only 10.1% of participants reported that they would decline the PCS test if it were offered to them. Another 22.4% of participants indicated that they were unsure about taking the test if PCS was offered to them.	84.5% of respondents were of reproductive age (18–44); 54% were females; 71.3% were in a relationship; 49.9% were parents; 70.6% of respondents had a future child wish; 59% were not religious; 37% completed university.
Propst *et al.* 2018	79 conditions with the option of adding fragile X	Pregnant women who had been offered an ECS test (N = 80). The out-of-pocket cost of the test was up to $350, unless covered by medical insurance.	Uptake of ECS; Reasons for accepting or declining testing	Forty individuals (50%) accepted, and 40 (50%) declined the offer.	92.5% of women were under 40 years old; 70.9% of respondents were non-Hispanic white; 53.8% of women did not yet have children; 87.5% had a Bachelor's degree or higher; 75% of respondents did not have any previous carrier screening.
Spencer *et al.* 2018	Hypothetical generic test panel	Adoptees aged 18 years or older. (n = 124)	Intention to participate in preconception ECS	76% of participants said they would want to have the test.	Mean age was 44 years (SD 14.7); 88% of the study population was female; 74% of respondents were Caucasian and 11% Asian/Pacific Islande; 59% of participants had at least a Bachelor's degree; 60% of respondents were married or in a committed relationship; 65% had children and 63% reported not to have a future child wish.
Schuurmans *et al.* 2018	50 serious recessive conditions	Non-pregnant women aged 18–40 years who were offered a couple-based ECS free of charge in the research context. (N = 190)	Uptake of ECS	117 couples accepted the offer. True uptake rate cannot be measured, as it is not possible to determine how many invitees were eligible to participate.	/
Nijmeijer *et al.* 2019	Hypothetical test panel for 50 diseases	Dutch individuals of reproductive age (18–45 years). (n = 781)	Intention to participate in preconception ECS	Of all participants, 31% reported that they probably or certainly would take a preconception ECS test. Another 36% did not want to be tested and 33% were uncertain.	Mean age was 31.2 years (SD 7.33); 49% of respondents were female; 33% had a high educational level; 54% had religious beliefs; 75% of respondents were married or in a relationship; 41% were considering a (future) pregnancy; 3% was currently pregnant.

(Continued)

Table III Continued.

Study	Composition of test panel	Study population	Reported measures relevant to ECS	Main findings	Participants characteristics
Larsen et al. 2019	> 100 conditions	Women who had a prenatal or preconception genetic counseling encounter. (n = 483)	Uptake of ECS	An overall acceptance rate of 39.8% was found. A significantly higher proportion of women counseled preconception (68.7%) accepted the ECS compared with those women seen during pregnancy (35.1%).	43.9% were Caucasian, 17.6% Hispanic and 13.7% African American; 76.2% of women were younger than 35 years.

/ indicates information not provided

studies ($n = 10$) used a survey methodology with a custom developed questionnaire. The other two remaining studies used a retrospective medical record review.

Main findings

The main study findings of this systematic review are summarized in Table III, including the composition of the test panel, the outcome measures used and some key figures on participants' characteristics.

Intention to take a (hypothetical) ECS test

Attitudinal studies gauging respondents' interest in a hypothetical ECS test have yielded diverging results. For example, while surveys conducted in Sweden (Ragnar et al., 2016) and the Netherlands (Plantinga et al., 2016; Nijmeijer et al., 2019) found that approximately one-third of the respondents would consider ECS, in an Australian study (Ong et al., 2018) about two-thirds of the surveyed individuals indicated interest in a hypothetical ECS test for a large number of recessive disorders. The authors of the Australian study attribute this finding to the media attention to preconception carrier screening in Australia. However, they also note that in their study population, the willingness to undergo ECS was associated with the nature of disorders to be included in the test. For example, 92% of the respondents interested in ECS indicated they would take ECS if the test included diseases affecting the lifespan of children or infants. By contrast, 61% would take the test if ECS were performed for adult-onset disorders. In the Dutch study of Plantinga et al. (2016), the age of onset of the screened disorders was not found to influence respondents' intentions to consider ECS. However, respondents were less likely to express interest in ECS for non-health-related predispositions (e.g. athletic ability).

Other studies in Belgium (Chokoshvili et al., 2017) and the USA (Briggs et al., 2017) reported that 54% and 49% of the respondents, respectively, expressed interest in preconception carrier screening. The highest intention to participate in preconception ECS was observed in the study of Spencer et al. (2018) where adopted individuals were surveyed. Although only 56% of the respondents were considered to be of reproductive age (i.e. <43 years Female; <50 years Male), 76% of all respondents indicated interest in ECS. Curiosity and the desire to inform other biological relatives (such as a child or sibling) were the most frequently cited reasons for showing interest in ECS (Spencer et al., 2018). No statistically significant difference was found for indicated interest between participants having some knowledge of their family medical history and those without any knowledge (Spencer et al., 2018).

Four out of twelve studies reported on the proportion of respondents that were undecided or uncertain about having ECS (Plantinga et al., 2016; Ragnar et al., 2016; Ong et al., 2018; Nijmeijer et al., 2019). In the Dutch study by Plantinga et al. (2016) just over half of respondents (51%) were undecided regarding whether they would be willing to participate if ECS were offered to them. Likewise, 42% of Swedish parents surveyed as part of the Swedish Pregnancy Planning (SWEPP) study were uncertain about having ECS prior to a pregnancy (Ragnar et al., 2016). In the Australian study of Ong et al. (2018), 22% of participants were unsure about whether they would take a preconception ECS test. Finally, 33% of all respondents were uncertain if they would take a preconception ECS test in the Dutch study by Nijmeijer et al. (2019).

Uptake of ECS

Studies reporting the actual uptake of ECS offers among prospective parents ($n = 4$) have found variable uptake rates (8%–50%) in ECS across different study populations. Gilmore et al. (2017) found that 34% of women who were offered a preconception ECS test free of charge in a research setting accepted the offer. The main reasons for declining participation included lack of time, lack of interest and not wanting the information. Another study of Propst et al. (2018), found that 50% of a cohort of 80 pregnant women accepted an offer of an out-of-pocket ECS test (expenses that are not reimbursed by health insurance). The most cited reasons for declining ECS in this study were lack of family history, low perceived risk of being a carrier couple and the fact that results would not influence their reproductive choices in (future) pregnancies. The main reasons for accepting the commercial offer were the desire to learn about the risk of having a child affected with a recessive condition, interest in genetic information and seeking the ability to make informed decisions regarding pregnancy (Propst et al., 2018). The uptake for an out-of-pocket ECS (8%) offer was considerably lower among couples with primary or secondary infertility in an earlier study by Higgins et al. (2015). However, the authors noted that the uptake had increased from 3.3% to 17.5% during the

Table IV Factors influencing the interest in and uptake of ECS.

	Higgins et al. (2015)	Plantinga et al. (2016)	Ragnar et al. (2016)	Chokoshvili et al. (2017)	Briggs et al. (2017)	Gilmore et al. (2017)	Ong et al. (2018)	Propst et al. (2018)	Spencer et al. (2018)	Schuurmans et al. (2018)	Nijmeijer et al. (2019)	Larsen et al. (2019)
Socio-demographic factors												
Gender		NS	NS	NS			NS				NS	
Age		SA ($p = 0.040$)	SA (female $p = 0.04$)	SD ($p < 0.01$)		SA ($p < 0.001$)	NS	NS	NS		NS	NS
Relationship status		NS				NS	NS				NS	
Employment status						NS						
(Household) Income			NS			SA ($p = 0.001$)	SA ($p = 0.030$)					
Education level		NS	NS	SD ($p < 0.01$)		SA ($p < 0.001$)	SA ($p = 0.033$)	NS	NS		NS	
Religion		SA ($p < 0.001$)		NS			SA ($p = 0.03$)				SD ($p = 0.034$)	
(Self-reported) Ethnic Background						NS		SA ($p = 0.003$)				NS
Medicaid						NS						
Factors related to reproduction												
Having Children						SA ($p = 0.029$)		NS	NS			NS
Previous miscarriage			NS					NS				NS
(Future) Child Wish		NS					NS		NS		SD ($p = 0.011$)	
Pregnancy Planning			SA (male $p = 0.01$)									
Prenatal Diagnostics			SA (male & female $p < 0.001$)									
Gestational Age												SA ($p < 0.001$)
Twin Pregnancy												NS
Wanting to know the sex of the baby			SA (female $p < 0.001$)									
Gender selection			SA (female $p < 0.001$)									
Pursuing assisted reproductive technology												SA ($p < 0.001$)
Pregnancy through egg and/or sperm donation												NS

(Continued)

Table IV Continued.

	Higgins *et al.* (2015)	Plantinga *et al.* (2016)	Ragnar *et al.* (2016)	Chokoshvili *et al.* (2017)	Briggs *et al.* (2017)	Gilmore *et al.* (2017)	Ong *et al.* (2018)	Propst *et al.* (2018)	Spencer *et al.* (2018)	Schuurmans *et al.* (2018)	Nijmeijer *et al.* (2019)	Larsen *et al.* (2019)
Factors related to genetic screening												
Previous carrier screening						NS		NS				
Indication for genetic counseling												NS
Genetic condition in the family						SA ($p < 0.001$)						NS
Knowing someone with a genetic condition						SA ($p < 0.001$)					NS	
Prior knowledge/awareness of ECS							SA ($p < 0.001$)					
Know about it from family members							SA ($p < 0.01$)					
Know about it through searches on the internet							SA ($p < 0.048$)					
Genetic knowledge							SA ($p < 0.005$)					
Other factors												
Cost of testing	SD											

SD: significant difference
SA: significant association
NS: not significant

observation period (2010–2013) following the reduction of out-of-pocket cost associated with the ECS test.

Larsen *et al.* (2019) retrospectively reviewed medical records of women who had a prenatal or preconception genetic counseling session at a large academic genetic counseling service in an urban private hospital-based outpatient clinic and observed an overall ECS uptake rate of 39.8%. Significantly more women counseled preconception (68.7%; $n = 67$) accepted ECS compared to women who were counseled during pregnancy (35.1%; $P < 0.001$; $n = 416$). The highest acceptance rate within this study was measured among women who were counseled preconception in preparation for IVF (74.5%; $n = 38/51$). Within the prenatal group, women counseled at an earlier gestational stage were also more likely to accept testing (Larsen *et al.*, 2019).

In a more recent study conducted in the Netherlands, 4295 women were invited to participate in a preconception ECS offer for couples, which resulted in 117 couples undergoing screening. While this number suggests low uptake, the exact uptake rate could not be documented as some invitees may not have been eligible to participate (for example because they were single) (Schuurmans *et al.*, 2018).

Factors influencing interest and uptake of ECS

Multiple studies included in this review have looked into various factors that could possibly influence the decision to accept or decline ECS. An overview of the factors studied and the results can be found in Table IV.

Socio-demographic factors

Gender, relationship status, employment status and having Medicaid insurance were not identified to be associated with the intention to undergo a (hypothetical) ECS test or uptake of an actual carrier screening offer. In contrast, associations between the decision to accept or decline ECS and other socio-demographic factors, such as age, religion, income, education level or ethnicity, were identified by at least one study included in this review.

In the study of Gilmore *et al.* (2017), younger women were more likely to decline an ECS offer. Younger respondents were also more often undecided about preconception ECS in the study of Plantinga *et al.* (2016). Furthermore, increased age was positively associated with the interest in preconception ECS in the studies by Ragnar *et al.* (2016) and Chokoshvili *et al.* (2017). However, not all of the primary studies identified age as an influencing factor. Age was not found to be associated with acceptance rates for ECS in six other studies (Ong *et al.*, 2018; Propst *et al.*, 2018; Spencer *et al.*, 2018; Larsen *et al.*, 2019; Nijmeijer *et al.*, 2019).

Three studies reported on an inverse relation between religion and the intention to participate in preconception ECS. Respondents with religious beliefs were less likely to be interested compared to non-religious respondents (Plantinga *et al.*, 2016; Ong *et al.*, 2018; Nijmeijer *et al.*, 2019). In the Belgian study by Chokoshvili *et al.* (2017), religion was not found to be an influencing factor when respondents were asked if they would consider having a carrier screening test together with their partner.

The interest in and uptake for ECS was positively associated with income in the studies by Gilmore *et al.* (2017) and Ong *et al.* (2018). Participants with a higher income were more likely to show interest in or accept an ECS offer. Conversely, household income was not found to influence parents' interest in preconception ECS in the Swedish study by Ragnar *et al.* (2016).

Decliners of an ECS offer were found to be less educated compared to acceptors in the study of Gilmore *et al.* (2017). In contrast, a negative association between education level and interest in ECS was found in the studies of Chokoshvili *et al.* (2017) and Ong *et al.* (2018); within these studies, less educated respondents were more likely to show interest in ECS. However, in five other studies included in this review, the education level of respondents was reported not to influence the interest in ECS (Plantinga *et al.*, 2016; Ragnar *et al.*, 2016; Propst *et al.*, 2018; Spencer *et al.*, 2018; Nijmeijer *et al.*, 2019).

In the study of Propst *et al.* (2018) white non-Hispanic individuals (60.7%) were more likely to accept ECS compared to non-white individuals (21.7%; $P = 0.003$). Other studies by Gilmore *et al.* (2017) and Larsen *et al.* (2019) reported no difference between women who accepted and who declined ECS across races/ethnicities. However, in the study of Larsen *et al.* (2019), where the retrospective medical record review identified a diverse population of women, some differences were noted, although these were statistically non-significant. Women of Ashkenazi Jewish decent were more likely to accept ECS ($n = 7/12$; 58.3%; $P = 0.195$) than women of Asian descent ($n = 12/41$; 29.3%; $P = 0.186$) or mixed ethnicities ($n = 7/25$; 28.0%; $P = 0.241$) (Larsen *et al.*, 2019).

Factors related to reproduction

Women who already had children were more likely to decline ECS in the study of Gilmore *et al.* (2017). However, Propst *et al.* (2018), Spencer *et al.* (2018) and Larsen *et al.* (2019) observed no significant associations between the interest or uptake of ECS and the number of children or pregnancies. Respondents with a (future) child wish were more likely to show interest in ECS in the study of Nijmeijer *et al.* (2019). Three other studies (Plantinga *et al.*, 2016; Ong *et al.*, 2018; Spencer *et al.*, 2018) did not identify a significant association between child wish and the intention to have ECS. Finally, women pursuing ART to get pregnant were more likely to accept ECS in comparison to women who got pregnant with the help of ART but who were not offered ECS (Larsen *et al.*, 2019).

Within the study cohort of the SWEPP study, women's interest in preconception ECS was positively associated with having undergone prenatal diagnostics, wanting to know the sex of the baby prior to the delivery and having positive attitudes toward fetal sex selection. Furthermore, the male partners' interest was associated with having had a planned pregnancy and having undergone prenatal diagnostics (Ragnar *et al.* 2016).

Other examined factors that were not found to be associated with interest/uptake in ECS were previous miscarriage (Ragnar *et al.*, 2016; Propst *et al.*, 2018; Larsen *et al.*, 2019), twin pregnancy (Larsen *et al.*, 2019) and a pregnancy established through egg and/or sperm donation (Larsen *et al.*, 2019).

Factors related to genetic screening

Knowing someone with a genetic condition or having a family member with a genetic condition was positively associated with the uptake of ECS in the study of Gilmore *et al.* (2017). In contrast, Nijmeijer *et al.* (2019) reported that knowing someone with a genetic condition was not associated with the intention to participate in ECS. Likewise, a positive maternal and/or paternal family history of genetic disease was

not associated with ECS acceptance rates in the retrospective medical record review by Larsen et al. (2019). In the same study, the indication for genetic counseling during pregnancy (e.g. advanced maternal age or abnormal ultrasound result) was also not significantly associated with the uptake of ECS. Having undergone previous carrier screening (Propst et al. 2018) or receiving positive CF test results (Gilmore et al., 2017) also did not influence the uptake of ECS.

Ong et al. (2018) identified several (genetic) knowledge factors that were associated with the intention to have preconception ECS. Respondents who had prior knowledge or awareness of ECS were more likely to be sure of their intention to either accept or decline ECS. Their study results also show that people who knew about ECS from family members or through internet searches were more likely to show interest in ECS. In addition, the likelihood of accepting ECS was higher for respondents with 'high', 'good' or 'some' genetic knowledge compared to those with 'low' genetic knowledge.

Other related factors

A potentially interesting factor that was investigated in some of the studies included in this review is the impact of the cost of testing and/or insurance coverage. Plantinga et al. (2016) reported that 58% of respondents would be willing to pay for ECS, with a median cost of €75. Nearly half of the adoptees surveyed by Spencer et al. (2018) were willing to pay $1 to $100 for ECS themselves. In the study of Briggs et al. (2017), 28% of participants were unwilling to pay out-of-pocket and 37% of participants were willing to pay at least $50 to $100. In the Australian study by Ong et al. (2018), 19% of respondents would do ECS for free, 22% would be willing to pay <$AUD 50 and another 34% would do ECS if it would cost between $AUD 50 and $AUD 200. Finally, only 9% of individuals surveyed by Nijmeijer et al. (2019) were willing to pay for ECS themselves. In the same study, 55% of respondents agreed that ECS should be completely reimbursed by health insurance.

The out-of-pocket cost (max. US $350—if insurance did not cover the test) did not seem to have an impact on the decision of test acceptors in the study of Propst et al. (2018). However, 15% of test decliners in the same study indicated 'Insurance might not cover the full cost of testing' as a reason for declining ECS. Gilmore et al. (2017) found no significant difference between women who declined or accepted ECS based on insurance type (Medicaid or not). The impact of the cost of testing/insurance type on the decision-making process could not be addressed in the study of Larsen et al. (2019).

Discussion

Results of the attitudinal studies around ECS suggest that there is considerable interest in ECS among (reproductive age) individuals in the general population (Plantinga et al., 2016; Ragnar et al., 2016; Briggs et al., 2017; Chokoshvili et al., 2017; Ong et al., 2018; Spencer et al., 2018; Nijmeijer et al., 2019). However, our findings show that actual test uptake among prospective parents (Higgins et al., 2015; Gilmore et al., 2017; Propst et al., 2018; Schuurmans et al., 2018; Larsen et al., 2019) is substantially lower. These results support the idea that self-reported intention to have ECS does not always translate into actual uptake when ECS is offered. The psychosocial aspects of genetic testing have been studied previously in the area of familial cancer syndromes and Huntington's disease (HD). In the case of HD, the intention of at-risk individuals to take a predictive genetic test for HD tends to be high (70–80%), while uptake rates tend to be much lower (10–20%). A real opportunity to learn genetic information seems to be more difficult to process and less appealing compared to a hypothetical test offer (Lerman et al., 2002; Sheeran and Webb 2016). This phenomenon is well documented in the literature as the 'Intention–Behavior Gap'. This theory states that three pivotal tasks must be accomplished to secure intention realization: people need to initiate, maintain and close goal pursuit (Sheeran and Webb 2016). Having the intention to undergo a (hypothetical) ECS test can be seen as part of the initiation phase, but not everyone who initiates a goal pursuit will eventually close it. Many internal and external factors can possibly influence actual behavior, whereby the behavior might no longer correlate with the values and attitudes of the individual. For instance, the out-of-pocket cost of testing might persuade someone to decline despite his interest in ECS. The results of the studies focusing on the intention to take a (hypothetical) ECS test show that a considerable proportion of respondents are willing to pay for ECS themselves. However, the amount they are willing to pay is considerably lower than actual prices for ECS panels currently being offered.

In the study of Gilmore et al. (2017), test decliners more commonly cited lack of interest and lack of time as reasons to decline an ECS offer. A similar result was observed in a theory-guided review by Chen and Goodson (2007) where lack of time was the factor most frequently associated with the decision to decline CF carrier screening. However, caution is needed when interpreting these statements as practical or logistical reasons given for declining ECS might also mask reasons not mentioned by respondents. Participants might be hesitant to discuss more personal reasons with researchers they are not familiar with (Gilmore et al., 2017). It is possible that participants would have made other decisions regarding ECS in a more clinical context in interaction with health care providers with whom they have a relationship of trust. The influence of health care providers and/or a perceived difficulty or inability to refuse ECS as an influencing factor in the decision-making of patients were identified in multiple studies included in the systematic reviews of Chen and Goodson (2007) and Ioannou et al. (2014b). Health care providers should be aware of this possible influence when informing prospective parents to make sure that couples are feeling able to refuse ECS when they are not interested.

Information gained through ECS might be perceived as irrelevant by test decliners because of the low perceived risk of being a carrier based on their personal or family history (Chen and Goodson 2007; Ioannou et al., 2014a; Propst et al., 2018). Lack of family history was also found to be one of the strongest predictors of declining carrier screening in earlier studies focusing on single gene carrier screening (Chen and Goodson 2007; Ioannou et al., 2014b). In the study of Gilmore et al. (2017) test-intending non-participants were more likely to decline the offer because of privacy- or discrimination-related concerns and emotional reasons. It is possible that the extensive amount of information regarding ECS in the informed consent form that was sent to them might have influenced their decision to opt-out, given the fact that these women previously had accepted CF carrier screening (Gilmore et al., 2017). Providing multiple opportunities for prospective participants to learn information and ask questions might facilitate informed decision-making because it allows prospective parents to think and reflect about their future reproductive plans before accepting or declining ECS (Robinson et al., 2016; Gilmore et al., 2017).

Following the recommendation of the ACMG (ACOG 2017), more efforts should be made to establish services where ECS can be offered and discussed with couples planning a pregnancy.

The highest overall uptake was observed in a study where ECS was offered to pregnant women (Propst *et al.*, 2018). In contrast, most studies focusing on preconception ECS reported lower overall uptake rates. Similar results have been reported within the context of population-based CF carrier screening, where preconception screening was generally associated with lower uptake rates compared to prenatal screening (Ioannou *et al.*, 2014b; Henneman *et al.*, 2016). Based on these findings it appears that potential users may perceive carrier screening to be more immediately relevant and useful during pregnancy. However, an exception to this general pattern was reported in the study of Larsen *et al.* (2019), in which significantly more women who were counseled preconception (68.7%) accepted ECS, compared to women who were counseled during pregnancy (35.1%) (Larsen *et al.*, 2019). Within the group counseled prior to conception, the highest acceptance rate (74.5%) was observed among women who were counseled preconception in preparation for IVF ($n = 51/67$) (Larsen *et al.*, 2019). Furthermore, non-pregnant women planning to pursue IVF were significantly more likely to accept ECS compared to women who became pregnant following IVF. One potential explanation for this finding, also suggested by the authors themselves, is that physicians might be more inclined to actively direct patients preparing for IVF to have ECS because of the immediate availability of PGT following positive screening results (Larsen *et al.*, 2019). However, this group might also be more interested in ECS prior to conception as they are already undergoing fertility treatment and thus ECS in combination with PGT might be perceived as part of the ongoing treatment.

Studies included in this review explored the interest in ECS among individuals and couples in the general population. Differences in the outcome measures might also be explained by heterogeneity across the surveyed populations or the recruitment methods of these studies. While some studies focused on exploring the views of respondents in a reproductive context (couples planning a pregnancy, couples undergoing fertility evaluation or treatment, pregnant women, women attending a preconception consultation), other studies surveyed a much more demographically diverse population where respondents were not always of reproductive age (Chokoshvili *et al.*, 2017; Ong *et al.*, 2018; Spencer *et al.*, 2018). Even though professional guidelines are clearly stating that ECS should be available to couples considering pregnancy or already pregnant, studies focusing on the views of demographically diverse populations can also give valuable insights. These results can contribute to the ongoing debate about the desirability and acceptability of offering ECS by offering a societal point of view.

The proportion of women who were undecided or uncertain about having ECS should not be ignored when assessing the interest in ECS. As ECS is a new and relatively unknown test for most future parents, the awareness and comprehension within the general population could be rather limited. Efforts should be made to ensure that prospective parents make decisions regarding ECS based on accurate and sufficient knowledge. Genetics professionals have expressed the need for adequate pre- and post-test counseling services that should be made available to couples considering ECS to ensure informed reproductive decision-making together with additional guidelines for primary health care professionals (Cho *et al.*, 2013; Lazarin *et al.*, 2016; Janssens *et al.*, 2017).

Study limitations

First, it is possible that some biases exist in the primary empirical studies of this review. Most of the studies included in this review used convenience sampling or targeted very specific groups within the population who were conveniently available to participate. It is possible that certain groups of people were more inclined to participate, for example individuals with more outspoken opinions on the topic (Delgado-Rodriguez and Llorca 2004). Consequently, the study findings should not be generalized. Second, by focusing on publications written in English, we might have missed relevant publications to include within this systematic review. Third, our search only identified studies from five Western countries. It is possible that populations in different countries may hold different views on ECS towing to differences in healthcare systems and differences in exposure to (critical) information (cultural bias) (Chokoshvili *et al.*, 2017). Sufficient attention should be made to this when drawing conclusions based on these findings.

Implications for future research

More research is needed to see if the observed trends also apply to a broader and more diverse population (Plantinga *et al.*, 2016; Gilmore *et al.*, 2017; Propst *et al.*, 2018). As only five studies have looked into the uptake of ECS there is a high need for more implementation studies. This would allow for an assessment of the extent to which individuals or couples make informed decisions regarding ECS and which factors (ease of access to testing, costs and reimbursement of testing, attitudes regarding pregnancy termination, etc.) are associated with informed decision-making. More prospective studies where ECS is offered to couples showing an interest in ECS could yield additional insights into the complexity of the intention–behavior gap and the decision-making process of couples regarding ECS. It will also allow us to gain a better understanding of the motives for or against ECS (among prospective parents), the concerns people might have toward ECS and the doubts people might experience when considering ECS.

To understand why certain individuals/couples are undecided or uncertain on whether or not they would like to participate in ECS, future research should try to synergize both quantitative and qualitative research methods: qualitative research may provide valuable insights into the decision-making process and experiences of patients in ways that quantitative analysis cannot. These results can be used to further facilitate responsible implementation of ECS and inform and guide healthcare providers interacting with prospective parents who are considering ECS.

Future research should also focus more on the impact of the costs of testing and/or insurance coverage on the decision-making process of couples considering ECS as this is likely to be an important factor.

Implications for practice

With the continued decline in the cost of ECS, combined with the growing number of recommendations of professional membership organizations, it is likely that the perceived value of ECS in the context of reproductive healthcare will continue to grow (Edwards *et al.*, 2015; Higgins *et al.*, 2015; Henneman *et al.*, 2016; Committee on Genetics 2017). Therefore, it is to be expected that an increasing number of couples in the general population will actively seek information about ECS and pursue testing in the future. Building a strong network of

preconception healthcare services through which screening could be offered could be a way to integrate ECS in a responsible way and to make sure that couples can learn about the possibility of having ECS prior to pregnancy. This will however demand a critical reflection on how to prioritize resources within preconception care (Ragnar *et al.*, 2016).

As ECS is a new and relatively unknown test for most future parents, the awareness and comprehension within the general population could be rather limited. In the coming years it will be very important to focus more on providing continuous high-quality information to the general public in order to improve genetic literacy, to reduce misconceptions and to manage expectations (Chokoshvili *et al.*, 2017; Ong *et al.*, 2018). Adequate pre- and post-test counseling services should be made available to couples being offered ECS to ensure informed reproductive decision-making. Complete and transparent information will help prospective parents in weighing the advantages and disadvantages associated with ECS so that they can make fully informed reproductive decisions (Ragnar *et al.*, 2016; Chokoshvili *et al.*, 2017).

Primary health care providers will have an important role to play when guiding couples who are planning a pregnancy through the available reproductive screening services (Ragnar *et al.*, 2016). Hence, there will be a growing need for widely accessible information and guidelines for primary health care providers alongside patient friendly genetic counseling tools (Larsen *et al.*, 2019).

Conclusion

The aim of this systematic review was to synthesize evidence from empirical studies that assess the interest in/uptake of ECS among individuals and couples in the general population. Results of the primary studies included in this review demonstrate that there is considerable interest in ECS among (reproductive age) individuals in the general population. However, actual uptake of ECS seems to be substantially lower than prospective parents' reported intentions to undergo ECS. In the included studies, 32–76% of respondents were interested in a (hypothetical) ECS test, while uptake rates for actual ECS offers ranged from 8% to 50%. The highest overall uptake was observed when ECS was offered to pregnant women (50%). By contrast, studies focusing on the preconception population reported lower overall uptake rates (8–34%) with the exception of one study where women were counseled preconception in preparation for IVF (68.7%).

Due to restricted nature of the samples and methods of the underlying primary studies, some of the reported results might not be transferable to a broader population. More research is needed to see if the observed trends also apply to a broader and more diverse population.

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Authors' roles

Jeffrey Cannon, Davit Chokoshvili, Eva Van Steijvoort and Pascal Borry designed the study. The comprehensive search approach, selection and screening of articles were carried out by Davit Chokoshvili and Eva Van Steijvoort. The quality appraisal was performed by Eva Van Steijvoort and Kathleen Holemans. A first draft of the article was written by Eva Van Steijvoort and critically discussed and revised by Jeffrey Cannon, Davit Chokoshvilil, Pascal Borry, Hilde Peeters, Karen Peeraer and Gert Matthijs. Pascal Borry coordinated the study. All the authors have approved the final version.

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Conflict of interest

The authors declare no conflict of interest.

References

ACOG. Committee opinion no. 690: carrier screening in the age of genomic medicine. *Obstet Gynecol* 2017;**129**:e35–e40.

Briggs A, Nouri P, Galloway M, Yaklic JL, Maxwell R, Lindheim S. Patients' awareness and attitudes towards genetic carrier screening. *Obstet Gynecol* 2017;**129**:88S–88S.

Chen LS, Goodson P. Factors affecting decisions to accept or decline cystic fibrosis carrier testing/screening: a theory-guided systematic review. *Genet Med* 2007;**9**:442–450.

Cho D, McGowan ML, Metcalfe J, Sharp RR. Expanded carrier screening in reproductive healthcare: perspectives from genetics professionals. *Hum Reprod* 2013;**28**:1725–1730.

Chokoshvili D, Belmans C, Poncelet R, Sanders S, Vaes D, Vears D, Janssens S, Huys I, Borry P. Public views on genetics and genetic testing: a survey of the general public in Belgium. *Genet Test Mol Biomarkers* 2017;**21**:195–201.

Chokoshvili D, Vears D, Borry P. Expanded carrier screening for monogenic disorders: where are we now. *Prenat Diagn* 2018;**38**:59–66.

Clayton EW, Hannig VL, Pfotenhauer JP, Parker RA, Campbell PW III, Phillips JA III. Lack of interest by nonpregnant couples in population-based cystic fibrosis carrier screening. *Am J Hum Genet* 1996;**58**:617–627.

Committee on Genetics. Committee opinion no. 691: carrier screening for genetic conditions. *Obstet Gynecol* 2017;**129**:e41–e55.

Delgado-Rodriguez M, Llorca J. Bias. *J Epidemiol Community Health* 2004;**58**:635–641.

Edwards JG, Feldman G, Goldberg J, Gregg AR, Norton ME, Rose NC, Schneider A, Stoll K, Wapner R, Watson MS. Expanded carrier screening in reproductive medicine-points to consider: a joint statement of the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal-Fetal Medicine. *Obstet Gynecol* 2015;**125**:653–662.

Gilmore MJ, Schneider J, Davis JV, Kauffman TL, Leo MC, Bergen K, Reiss JA, Himes P, Morris E, Young C *et al.* Reasons for declining preconception expanded carrier screening using genome sequencing. *J Genet Couns* 2017;**26**:971–979.

Hawker S, Payne S, Kerr C, Hardey M, Powell J. Appraising the evidence: reviewing disparate data systematically. *Qual Health Res* 2002;**12**:1284–1299.

Henneman L, Borry P, Chokoshvili D, Cornel MC, van El CG, Forzano F, Hall A, Howard HC, Janssens S, Kayserili H *et al.* Responsible implementation of expanded carrier screening. *Eur J Hum Genet* 2016;**24**:e1–e12.

Henneman L, Bramsen I, van Kempen L, van Acker MB, Pals G, van der Horst HE, Ader HJ, van der Ploeg HM, ten Kate LP. Offering preconceptional cystic fibrosis carrier couple screening in the absence of established preconceptional care services. *Community Genet* 2003;**6**:5–13.

Higgins A, Flanagan J, Von Wald T, Hansen KA. An expanded carrier screening tool enhances preconception cystic fibrosis screening in infertile couples. *Open J Obstet Gynecol* 2015;**5**:412–416.

Ioannou L, Massie J, Lewis S, McClaren B, Collins V, Delatycki MB. 'No thanks'-reasons why pregnant women declined an offer of cystic fibrosis carrier screening. *J Community Genet* 2014a;**5**:109–117.

Ioannou L, McClaren BJ, Massie J, Lewis S, Metcalfe SA, Forrest L, Delatycki MB. Population-based carrier screening for cystic fibrosis: a systematic review of 23 years of research. *Genet Med* 2014b;**16**: 207–216.

Janssens S, Chokoshvili D, Vears DF, De Paepe A, Borry P. Pre- and post-testing counseling considerations for the provision of expanded carrier screening: exploration of European geneticists' views. *BMC Med Ethics* 2017;**18**:46.

Kaback MM. Population-based genetic screening for reproductive counseling: the Tay–Sachs disease model. *Eur J Pediatr* 2000;**159**: S192–S195.

Larsen D, Ma J, Strassberg M, Ramakrishnan R, Van den Veyver IB. The uptake of pan-ethnic expanded carrier screening is higher when offered during preconception or early prenatal genetic counseling. *Prenat Diagn* 2019;**39**:319–323.

Lazarin G, Detweiler S, Nazareth S, Ashkinadze E. Genetic Counselors' perspectives and practices regarding expanded carrier screening after initial clinical availability. *J Genet Couns* 2016;**25**:395–404.

Lazarin GA, Haque IS, Nazareth S, Iori K, Patterson AS, Jacobson JL, Marshall JR, Seltzer WK, Patrizio P, Evans EA *et al.* An empirical estimate of carrier frequencies for 400+ causal Mendelian variants: results from an ethnically diverse clinical sample of 23,453 individuals. *Genet Med* 2013;**15**:178–186.

Lerman C, Croyle RT, Tercyak KP, Hamann H. Genetic testing: psychological aspects and implications. *J Consult Clin Psychol* 2002;**70**: 784–797.

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009;**6**:e1000100.

Nijmeijer SCM, Conijn T, Lakeman P, Henneman L, Wijburg FA, Haverman L. Attitudes of the general population towards preconception expanded carrier screening for autosomal recessive disorders including inborn errors of metabolism. *Mol Genet Metab* 2019;**126**:14–22.

Ong R, Howting D, Rea A, Christian H, Charman P, Molster C, Ravenscroft G, Laing NG. Measuring the impact of genetic knowledge on intentions and attitudes of the community towards expanded preconception carrier screening. *J Med Genet* 2018;**55**:744–752.

Plantinga M, Birnie E, Abbott KM, Sinke RJ, Lucassen AM, Schuurmans J, Kaplan S, Verkerk MA, Ranchor AV, van Langen IM. Population-based preconception carrier screening: how potential users from the general population view a test for 50 serious diseases. *Eur J Hum Genet* 2016;**24**:1417–1423.

Poppelaars FA, van der Wal G, Braspenning JC, Cornel MC, Henneman L, Langendam MW, ten Kate LP. Possibilities and barriers in the implementation of a preconceptional screening programme for cystic fibrosis carriers: a focus group study. *Public Health* 2003;**117**: 396–403.

Propst L, Connor G, Hinton M, Poorvu T, Dungan J. Pregnant women's perspectives on expanded carrier screening. *J Genet Couns* 2018;**27**:1148–1156.

Ragnar ME, Tyden T, Kihlbom U, Larsson M. Swedish parents' interest in preconception genetic carrier screening. *Upsala J Med Sci* 2016;**121**:289–294.

Robinson JO, Carroll TM, Feuerman LZ, Perry DL, Hoffman-Andrews L, Walsh RC, Christensen KD, Green RC, McGuire AL. Participants and study decliners' perspectives about the risks of participating in a clinical trial of whole genome sequencing. *J Empir Res Hum Res Ethics* 2016;**11**:21–30.

Ropers HH. On the future of genetic risk assessment. *J Community Genet* 2012;**3**:229–236.

Schuurmans J, Plantinga M, Lucassen A, Fenwick A, Abbott K, Birnie E, van Langen IM, Ranchor O. Short and long-term psychological impact of an active GP-provided couple-based ECS test-offer in the Dutch general population. 2018. (Conference abstract)

Sheeran P, Webb TL. The intention–behavior gap. *Soc Personal Psychol Compass* 2016;**10**:503–518.

Spencer S, Ewing S, Calcagno K, O'Neill S. Adopted individuals' views on the utility and value of expanded carrier screening. *J Genet Couns* 2018;**27**:1341–1348.

Srinivasan BS, Evans EA, Flannick J, Patterson AS, Chang CC, Pham T, Young S, Kaushal A, Lee J, Jacobson JL *et al.* A universal carrier test for the long tail of Mendelian disease. *Reprod Biomed Online* 2010;**21**:537–551.