Title: How does carrier status for recessive disorders influence reproductive decisions? A systematic review of the literature

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ABSTRACT

Introduction: Carrier screening for recessive disorders is undertaken by prospective parents to inform their reproductive decisions. With the growing availability of affordable and comprehensive expanded carrier screening (ECS), it is expected that carrier screening will become a standard practice in the future. However, the impact of positive carrier screening results on the reproductive decisions of at-risk couples (ARCs) remains underexplored.

Areas covered: We performed a systematic literature review to identify peer-reviewed publications describing reproductive decisions of ARCs. Our search identified 19 relevant publications spanning the period 1994 - 2018. By synthesizing available evidence, we found that most ARCs chose to prevent the birth of an affected child and the decision to utilize preventive reproductive options was strongly influenced by the clinical nature of a disorder. However, there was also some heterogeneity in reproductive decisions within the same recessive disorders, suggesting that choices of ARCs can be influenced by factors other than the clinical nature of a disorder.

Expert opinion: ECS is becoming increasingly common, which will result in the routine identification of many ARCs. Reproductive decision-making by ARCs is a complex and emotionally challenging process, highlighting the critical role of genetic counseling in the care for these potentially vulnerable patients.

Key words: expanded carrier screening, recessive disorders, reproductive decisions, at-risk pregnancy, prenatal diagnosis, pre-implantation genetic testing.

1. INTRODUCTION

Carrier screening is a form of genetic testing that aims to identify couples at risk of having a child with a recessive (autosomal or X-linked) genetic disorder [1]. In autosomal recessive disorders, both reproductive partners of an at-risk couple carry a pathogenic mutation in the same gene, while in X-linked recessive disorders, only the female member of the couple is a carrier. These at-risk couples (ARCs; also referred to as 'carrier couples') have a one-in-four chance of conceiving an affected child with the disorder in each pregnancy [2]. However, because they are typically healthy and lack family history for the disorder, ARCs are usually unaware of their reproductive risk until their child is diagnosed with the disorder [3]. The goal of carrier screening is to identify unsuspecting ARCs prospectively, ideally prior to conception, to allow them to make informed reproductive choices. Carrier couples who learn about their risk before pregnancy can choose from several reproductive options, including: deciding against having biological children with their current partner, undergoing in-vitro fertilization (IVF) with pre-implantation genetic testing (PGT) or using donor gametes, or accepting their risk and proceeding with a natural pregnancy. For ARCs who are already pregnant, options are limited to deciding whether to undergo prenatal diagnosis (PNDx), potentially followed by pregnancy termination if the fetus is affected [4].

The first carrier screening initiatives commenced more than 40 years ago with carrier screening offers for heritable recessive disorders such as Tay-Sachs disease (TSD) among the Ashkenazi Jewish community and sickle cell anemia in several Mediterranean countries [5, 6]. The reason behind these early initiatives was a relatively high prevalence of certain life-threatening genetic disorders among select ethnic groups, which created a need for identifying couples at risk of having affected children [7]. Ethnicity-based carrier screening programs were well-received by prospective parents and they became an integral part of family planning in many ethnic communities [8]. In the subsequent decades, as genetics of more recessive disorders were elucidated and the costs of molecular testing diminished, it became feasible to incorporate additional disorders into carrier screening tests. Following the adoption of next-generation sequencing (NGS) in the mid-2000s, screening for large number of recessive disorders in a single test became feasible, leading to the development of expanded carrier screening (ECS) [9].

ECS tests, which typically screen for more than 100 disorders, are currently available to prospective parents through various commercial providers [9]. Unlike traditional carrier

screening tests, ECS is not limited to disorders or mutations predominantly observed within specific ethnic groups, allowing ECS to identify carriers of recessive disorders in the general population, regardless of ethnicity [10]. At the same time, the cost of ECS has been steadily declining, making testing increasingly affordable for prospective parents [11]. Since 2015, several authoritative medical professional organizations have recognized the benefits of ECS, recommending that ECS be made available to couples planning a pregnancy or already pregnant [1, 12, 13].

It has been estimated that in the United States alone, approximately 200,000 ECS tests are performed annually [14]. As the availability and accessibility of ECS grows, an increasing number of couples are exposed to the choice of using this test. Consequently, the uptake of ECS is likely to further increase, with ECS potentially becoming a routine test performed in the reproductive context. Given that a comprehensive ECS test could identify 1-5% of couples as being at risk of having an affected child [15, 16], a large number of couples in the general population may receive positive results following an ECS. When a couple discovers they are an ARC, they could be prompted to make decisions about their newfound reproductive risk. It is important for healthcare providers to understand how carrier couples might process this information, what decisions they could face, and what kind of support they will require. Therefore, the aim of this systematic review is to gain insights into the potential impact of ECS on the subsequent reproductive decision-making of ARCs, by reviewing the outcomes of different carrier screening offers described in the literature. This will contribute to a better understanding of the potential impact of positive carrier screening results on at-risk couples, including the extent to which such results may influence reproductive decision-making.

2. Methods

We conducted a systematic literature review to identify original research articles on carrier screening reporting reproductive decisions of couples and females identified as being at risk of having a child affected with an autosomal recessive and an X-linked recessive disorder, respectively.

The search for relevant research articles was carried out in four online databases (Pubmed, Web of Science, CINAHL, Cochrane Library) using the following search string: "carrier" AND (“testing"[tw] OR “screening” [tw]) AND (reproductive behavior [tw] OR reproductive choices [tw] OR reproductive decision-making [tw] OR outcomes [tw] OR clinical decision making

[tw]). Following the systematic search of the four databases, we additionally consulted references of the identified papers in order to find any remaining publications of relevance to our systematic review. To further ensure the comprehensiveness of our search strategy, we also carried out a related search using Google Scholar based on the studies identified through the systematic search. This review followed PRISMA guidelines for systematic reviews of medical literature [17].

In order to be included in this systematic review, studies should have reported reproductive decisions of carrier couples (in autosomal recessive disorders) and/or female individuals (in X-linked recessive disorders) who, through carrier screening, were found to be at risk of having an affected child. As our objective was to investigate how prospective parents in the general population may act on their carrier status information, we decided to exclude studies primarily focused on couples/individuals with previously known risk of having an affected child. For example, studies where prospective parents were referred for genetic testing due mostly to the family history of a specific recessive disease were excluded. Only full-length English-language articles published in peer-reviewed journals were included in this systematic review.

The search was undertaken in January 2019 and was carried out by two researchers (E.V.S. and D.C.) who worked independently and continually compared their findings to discuss the differences, if any.

3. RESULTS

The systematic literature search process is summarized in Figure 1 below. In total, the systematic search identified 17 distinct studies reported in 19 peer-reviewed publications describing reproductive choices of couples and females (in X-linked recessive disorders) at risk of having affected children [18-36]. The main characteristics of these studies are summarized in Table 1. Owing to the relative novelty of ECS, studies investigating the impact of positive carrier screening results on couples pursuing ECS specifically comprise a minority (3/17) of the studies included in this review. Consequently, most studies can be described as either ethnicity-specific or population-based, focused on single disorders such as cystic fibrosis (CF) or a handful of disorders relatively common in a certain population (e.g. [35]).

In most studies (15/17), the target population to whom carrier screening was offered comprised couples and individuals who were considering pregnancy or were already pregnant. In

autosomal recessive disorders, the most commonly employed screening strategy was the sequential or stepwise screening method, where screening is initiated in one member of a couple (typically the female), followed by screening of the reproductive partner only if the initial proband is found to be a carrier. This approach was particularly common in earlier, pre-ECS studies, in which participants were typically recruited through antenatal clinics and women's healthcare providers. Two notable exceptions were an ethnicity-based screening program targeting Ashkenazi Jewish population in Montreal, Canada [22], and a population-based carrier screening offer for hemoglobin disorders in France [25], both of which were aimed at high school students.

Reproductive decisions of carrier couples (in autosomal recessive disorders) and females (in X-linked recessive disorders) are summarized in table 2. Throughout the studies, the most commonly screened disorder was CF (10/17), having been offered both as a stand-alone test and as part of a wider panel. The vast majority of couples identified as carriers of CF took steps to prevent the birth of an affected child through PNDx followed by an elective termination of an affected pregnancy or, if identified preconceptionally, pursued IVF-PGT. However, studies also report cases where at-risk couples decided to accept their reproductive risk or chose not to terminate an affected pregnancy. While it was not always possible to determine how couples had arrived at specific reproductive decisions, in several cases, authors provided insightful comments that shed light on the reproductive decision-making process among such couples. For example, Levenkron et al. describe an ARC that declined PNDx, where the female stated she "had not thought through the 'consequences' of being at risk for a CF child prior to [screening]" and, following a more extensive deliberation, decided against PNDx as she "would not terminate an affected pregnancy" [21]. In another notable case discussed by Witt et al., a twin pregnancy was diagnosed with CF, with both concordant twins identified as homozygous for the Phi508del. mutation. The authors report that "[the] couple of the affected twin pregnancy chose to continue their pregnancy after lengthy deliberations and counseling" [23].

Similarly, in hemoglobin disorders, screening for which was described in 6 studies (including two studies utilizing ECS), at-risk couples typically underwent PNDx, and the majority of affected pregnancies were terminated. Most notably, in a large cohort of couples in the study of Tongsong et al., the proportion of at-risk couples who pursued PNDx and the proportion of affected pregnancies that were terminated were 97% and 98%, respectively [31]. An exception to this general trend was observed by Colah et al., who noted that in their study, while all four pregnancies identified as affected were terminated, as many as 16/37 (43%) carrier couples did

not return to the clinic for PNDx. Although the authors mention distinct characteristics of their study population, such as low socio-economic status, they do not offer a clear explanation for the low uptake of PNDx [28]. In addition, as with CF, several studies on hemoglobin disorders included cases where at-risk couples knowingly declined to alter their reproductive plans. For example, Tongsong et al., and Mitchell et al. both report a single case where a couple was found to have an affected pregnancy and decided against pregnancy termination, delivering a child with Beta-thalassemia/HbE disease and Beta-thalassemia, respectively [22, 31].

Several studies provide insights into how medical characteristics of a disorder, such as severity, may affect reproductive decision-making of ARCs. For example, Zuckerman et al. reviewed reproductive outcomes of 83 couples identified as carriers of Gaucher disease (GD) in an Ashkenazi Jewish screening program in Israel, comparing outcomes of prospective parents across sub-types of GD [27]. The authors report that among couples at risk of having a child with the mild type 1 GD, PNDx was performed in 53/73 (73%) pregnancies and 2/13 (15%) of the affected pregnancies were electively terminated. In contrast, among the couples at risk of having a child with the moderate type 1 GD, PNDx was undertaken in 15/17 (88%) pregnancies and 2/3 (67%) affected pregnancies were electively terminated. Similarly, in two recent studies that surveyed carrier couples who had utilized a commercial ECS test, the nature of a disorder was found to be an important factor in determining the extent to which carrier couples acted on their test results. Ghiossi et al., whose sample comprised 64 carrier couples, compared reproductive decisions among three groups of carrier couples stratified by disease severity ("profound", "severe", and "mild"). They observed that 32/45 (71%) couples at risk of having a child with a disorder categorized as "profound" or "severe", reported having taken or planning to take an action, such as undergoing IVF-PGT or, if already pregnant, using PNDx. By contrast, in disorders categorized as "moderate" (e.g. Alpha-1 Antitrypsin Deficiency and GJB2-related non-syndromic hearing loss), 4/19 couples (21%) reported having acted or planning to act on the results. Additional comments provided by some respondents further illustrated that the perceived severity of the identified disorder played an important role in couples' decisions [34]. These findings were subsequently corroborated by Taber et al., whose study used a larger sample of carrier couples (N=391) identified through the same ECS test [36]. In particular, Taber et al. found that the proportion of the couples who had used or intended to use their test results to avert the birth of an affected child increased with severity, among both non-pregnant and pregnant couples, with differences between the "profound" and "moderate" groups being the most prominent.

Taber et al. also observed that carrier couples who had been identified during pregnancy (n=154) were significantly less likely to alter their reproductive plans than those who had received their test results preconceptionally (n=235). More specifically, approximately one-third of couples in the former group indicated having undergone prenatal diagnosis, as opposed to three-quarters of carrier couples identified preconceptionally electing to avoid the birth of an affected child, primarily through IVF-PGT. The authors partly attribute these findings to the fact that many couples in their study population were IVF patients at the time of screening, receiving treatment for infertility. They suggest the possibility that patients undergoing IVF may be willing to readily accept PGT as part of the artificial reproduction treatment, while at the same time displaying reluctance towards PNDx once a pregnancy has been achieved [36]. The willingness of IVF patients to undergo PGT was also discussed by Franasiak et al., who noted that pursuing PGT may be an appealing reproductive option for at-risk couples receiving IVF treatment, even for treatable and low-penetrant disorders [32].

Four studies (including two ECS-based studies) also discussed reproductive decisions around X-linked recessive disorders among at-risk females who typically lacked family or personal history suggestive of the disorder. Fragile X syndrome (FXS) was the X-linked recessive disorder for which reproductive decisions were most extensively documented, primarily through the studies of Cronister et al. and Archibald et al. In the former study, 22 female carriers of an expanded FMR1 allele were identified. This included 14 carriers of an intermediate FMR1 allele (45-55 CGG repeats) who were offered PNDx for a reason unrelated to FXS. Notably, among these females, 7 (50%) requested testing of their fetus specifically for FXS, despite having been counseled on the low probability of having an affected child. According to the authors, the decision of these females was motivated by the desire to gain reassurance [26]. In the study of Archibald et. al, which describes reproductive choices among carriers of premutation (55-200 CGG repeats) and full mutation (200< CGG repeats) FMR1 alleles, the majority of pregnant carriers (16/22; 73%) pursued PNDx. Subsequently, two fetuses were found to harbor a full mutation and both pregnancies were terminated. Two pregnant female carriers (2/22; 9%) declined PNDx and did not pursue any further testing of the fetus on the grounds that they perceived the risk of having an affected pregnancy as low or would not terminate an affected pregnancy (carriers of 55 CGG repeats and 72 CGG repeats, respectively) [33].

4. DISCUSSION

In this systematic review, we analyzed the reproductive decisions of couples and females identified to be at risk of conceiving a child with a recessive disorder (collectively referred to as carrier couples or at-risk couples (ARCs)).

Based on the reproductive outcomes among ARCs reported in different studies, it can be concluded that most ARCs used their carrier status information to inform their family planning decisions. There is considerable evidence indicating that the clinical nature of a disorder the future child is at risk for may influence the extent to which couples act on their carrier status information. For example, carrier screening offers for life-limiting conditions such as CF and hemoglobin disorders have revealed that the vast majority of couples at risk of having an affected child with these disorders utilized preventive reproductive options, such as IVF-PGT, or PNDx followed by pregnancy termination. However, the literature also describes a small number of cases in which ARCs chose to accept their reproductive risk and declined further testing, or underwent PNDx but decided against terminating an affected pregnancy. By the same token, in disorders associated with less severe clinical phenotypes, ARCs were generally less likely to alter their reproductive plans. Most notably, in the study of Zuckerman et al., while the majority of couples at risk of having a child with the mild type 1 GD pursued PNDx, only two of the eleven (15%) couples with an affected fetus elected to terminate the affected pregnancies [27]. This is a markedly low pregnancy termination rate of affected pregnancies compared to most studies included in the present review. Similarly, two studies with a large number of carrier couples who had undergone ECS found that ARCs at risk of having a child with milder recessive disorders were less likely to alter their reproductive plans, compared to carriers of more severe, life-limiting, or debilitating conditions [34, 36]. These results suggest that the clinical nature of a disorder may strongly influence reproductive decision-making of ARCs. It is probable that most carrier couples at risk of having a child with a mild or more clinically manageable disorder use their carrier status information to prepare for the care of an affected child, as opposed to altering their reproductive plans. However, given that studies also observed some heterogeneity in reproductive decisions within the same recessive disorders, it is also clear that the clinical nature of a disorder is not the only factor informing couples' choices. Because decisions around reproduction are intensely personal, ARCs may factor in other considerations such as their risk perception, their ability to care for a child with special needs, and their personal views regarding available reproductive options [37].

The reproductive decision-making process that carrier couples go through can be highly complex and emotionally challenging, as indicated by a small number of empirical studies around this matter. Three qualitative interview studies with couples at risk of having an affected child revealed that ARCs typically experienced shock upon learning their reproductive risks and endured significant emotional distress in the period following the receipt of test results. In particular, ARCs often reported experiencing grief, tainted mental image of their (future) family and, in some cases, strained personal relationships with family members. However, in the longer term, most couples found their carrier status information actionable and made adjustments to their reproductive plans, with many couples in retrospect expressing high degree of satisfaction over undergoing screening [35, 38, 39]. It should be noted, however, that these three qualitative studies focused on life-limiting disorders typically resulting in significant childhood-onset morbidity. By contrast, in milder disorders, such as type 1 GD, some ARCs interviewed by Zuckerman et al. several years following screening, expressed dissatisfaction for participating in carrier screening, with several couples who had terminated their affected pregnancies regretting their decision [40]. These findings highlight the importance of genetic counseling to ensure that ARCs are supported in dealing with their newfound carrier status. In this regard, the dual role of genetic counseling should be recognized, where genetic counselors both provide psychological support to ARCs and educate them regarding available reproductive options [41]. As ECS tests include a wide range of disorders with variable clinical characteristics, genetic counselors should be aware that the informational and psychosocial needs of ARCs will likely vary across disorders, requiring ever more personalized approaches to ensure that couples' needs are addressed. Ensuring that ARCs have access to the support of genetic counselors is an important part of the care of these potentially vulnerable patients.

Several studies included in this review found that many infertile and sub-fertile ARCs who had carrier screening performed as part of their infertility work-up readily accepted PGT. Notably, PGT was commonly pursued also for relatively mild, low-penetrant, and treatable disorders [32, 34]. This finding can be explained by several considerations. First, as the process of assisted reproduction already entails an array of medical interventions, integration of PGT into the IVF trajectory may be relatively uncomplicated, associated with little additional burden for the patient. Second, providers of assisted reproduction services may adopt a view whereby the conception of a child with any preventable genetic disorder, however mild, is considered an iatrogenic failure and should therefore be avoided through PGT [42, 43]. Third, given that PGT takes place prior to conception, it can be argued that selection of embryos based on their

predisposition to genetic diseases is less morally problematic than, for example, terminating an ongoing pregnancy for the same condition [42]. While these factors potentially explain the appeal of PGT for all recessive disorders in the context of IVF, authors have also raised concerns over potential inequalities due to the fact that couples undergoing assisted reproduction may have access to more comprehensive testing options than couples in the general population [42].

4.1 Limitations

The purpose of this review was to gain insights into reproductive choices of ARCs who learn about their reproductive risks through carrier screening. To this end, we only included studies reporting outcomes of carrier screening offers in the general population, that is, not limited to couples and individuals with a previously known risk for having a child with a specific recessive disorder. Nevertheless, in several population-wide carrier screening offers included in this review, some ARCs had a known increased risk prior to participating in screening. At the same time, these studies did not always indicate whether a particular ARC had a pre-existing known risk or had first learned about their reproductive risk through carrier screening. Previous research has found that reproductive decisions may differ significantly between ARCs with a known personal or familial history for a recessive disorder and those who first learn about their reproductive risk through carrier screening [44]. In the absence of this important information, we are limited in our ability to contextualize reproductive decisions of ARCs reported in the studies.

It should be noted that how prospective parents perceive the severity of a specific disease may change over time, particularly as new effective therapeutic interventions targeting the disease are developed. In several recessive diseases for which carrier screening has long been available, therapeutic options have improved over the past decades, resulting in increased life expectancy and better quality of life for patients. Potentially, this progress has implications for reproductive decision-making of carrier couples. As a particular recessive disease is perceived increasingly treatable through improving medical interventions, fewer carrier couples may be inclined to prevent the birth of a child with this disease. Instead, they may use their carrier status information to prepare for the birth of an affected child, in order to initiate treatment early in the newborn's life. This consideration potentially limits direct comparability of studies around

reproductive decision-making of carrier couples, if such studies have been carried out decades apart.

Finally, our systematic review only included studies published in English. As a consequence, it is possible that our search strategy failed to identify relevant publications in languages other than English. We sought to address this possibility by carefully reviewing references cited in the included articles, which did not lead to the identification of additional studies in other languages.

4.2 Conclusion

In this systematic review, we analyzed available evidence around reproductive decision-making of couples and female individuals at 1-in-4 risk of having a child with a recessive disorder (collectively referred to as at-risk couples – ARCs). By synthesizing reproductive outcomes reported in 19 publications, we found that most ARCs tended to act on their carrier status information, either through IVF-PGT or, if pregnant, using PNDx and subsequently deciding on whether to terminate an affected pregnancy. In general, studies showed that the clinical characteristics of a disorder, primarily its severity, significantly influenced the extent to which ARCs utilized preventive reproductive options. However, the studies also observed some heterogeneity in reproductive decisions within the same recessive disorders, suggesting that choices of ARCs can be determined by factors other than the clinical nature of the disorder. These findings highlight the importance of post-test genetic counseling and psychological support to ensure the provision of adequate care to ARCs.

Given the growing availability and accessibility of expanded carrier screening (ECS), healthcare professionals will increasingly be confronted by ARCs who receive a positive ECS test result. The insights gained through this systematic review shed more light on the reproductive decision-making process these couples undergo, which could better inform medical care provided to these potentially vulnerable patients.

5. EXPERT OPINION

Expanded carrier screening (ECS) is rapidly emerging as a new standard of care in reproductive medicine. The rise in ECS utilization is driven by a combination of different factors, including the growing interest in ECS among prospective parents, increasing coverage of testing by

insurance companies, and, more recently, endorsement from reputable professional medical societies.

Over the past few years, the size of ECS tests has grown to include several hundreds of recessive disorder genes which are typically analyzed using next-generation sequencing methods. The outcome of this expansion is a highly comprehensive ECS test capable of identifying reproductive risks in prospective parents for a wide range of recessive disorders. However, the psychosocial implications of such a comprehensive ECS for future parents are far from uncomplicated. On the one hand, couples who, following an ECS test, learn that they are not carriers of a recessive disorder, can be reasonably certain that they will not have an affected child, since their residual risk is extremely low. On the other hand, couples who receive a positive test result will be faced with difficult decisions. First, some of these couples will not be true biologic carriers; the purportedly pathogenic mutations they carry may currently be mis-classified and in reality not be causative of the disorder. This is particularly true in cases where low-penetrance mutations are involved. Since in the absence of family history for the disorder no additional predictive information is available, such couples will need to make reproductive decisions under considerable uncertainty. Second, some carrier couples will learn that the disorder their future child is at risk of inheriting is associated with mild and treatable clinical symptoms. As illustrated by carrier screening program for Gaucher disease in Israel, such couples may find it challenging to decide whether it is warranted to act on their carrier status information and may even regret that they underwent screening in the first place. Third, a portion of carrier couples will be at risk of having a child with a severely debilitating or lethal recessive disease. Arguably, these couples stand to benefit the most from ECS, and the vast majority of them will decide not to have an affected child. However, the emotional challenges associated with altering reproductive plans due to genetic risks should not be underestimated. Therefore, in all three scenarios, it is critical that couples are provided with adequate genetic counseling and continued psychological support throughout their reproductive trajectory.

It is safe to say that the ‘traditional’ carrier screening is disappearing, giving way to ECS. Going forward, we only expect the size of ECS panels to keep growing. Although there is an upper limit to the number of recessive disorders that can be added to ECS, it is highly likely that ECS tests of the future will also incorporate a sub-set of dominant and polygenic diseases. This is understandable: after all, the majority of prospective parents want to know as much as possible about their reproductive risks, whereas laboratories offering ECS tests strive to develop more comprehensive testing solutions than their competitors. What is critical to ensure is that these

developments are coupled with efforts aimed at improving medical and psychosocial care for those couples who receive positive ECS test results.

Declaration of interest

The authors have no 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. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References

1. Henneman L, Borry P, Chokoshvili D, et al. Responsible implementation of expanded carrier screening. Eur J Hum Genet. 2016; 24:e1-e12.
2. Metcalfe SA. Carrier screening in preconception consultation in primary care. J Community Genet. 2012; 3:193-203.
3. Cornel MC. A higher impact of less specific preconception carrier screening: a plea for a "one size fits all" approach? Journal of Xiangya Medicine. 2017; 2.
4. Borry P, Henneman L, Lakeman P, et al. Preconceptional genetic carrier testing and the commercial offer directly-to-consumers. Hum Reprod. 2011; 26:972-7.
5. Kaback MM. Population-based genetic screening for reproductive counseling: the Tay-Sachs disease model. Eur J Pediatr. 2000; 159 Suppl 3:S192-5.
6. Zlotogora J, Carmi R, Lev B, et al. A targeted population carrier screening program for severe and frequent genetic diseases in Israel. Eur J Hum Genet. 2009; 17:591-7.
7. De Wert GM, Dondorp WJ, Knoppers BM. Preconception care and genetic risk: ethical issues. J Community Genet. 2012; 3:221-8.
8. Scott SA, Edelmann L, Liu L, et al. Experience with carrier screening and prenatal diagnosis for 16 Ashkenazi Jewish genetic diseases. Hum Mutat. 2010; 31:1240-50.
9. Chokoshvili D, Vears D, Borry P. Expanded carrier screening for monogenic disorders: where are we now? Prenat Diagn. 2018; 38:59-66.**
   (The paper provides the most up-to-date review of the current ECS landscape)

10. Lazarin GA, Haque IS, Nazareth S, 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; 15:178-86.
11. Chokoshvili D, Vears DF, Borry P. Growing complexity of (expanded) carrier screening: Direct-to-consumer, physician-mediated, and clinic-based offers. Best Pract Res Clin Obstet Gynaecol. 2017; 44:57-67.
12. Edwards JG, Feldman G, Goldberg J, et al. 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; 125:653-62.
13. Rink B, Romero S, Biggio Jr JR, et al. Carrier Screening for Genetic Conditions. Obstet Gynecol. 2017; 129:E41-E55.
14. Lazarin GA, Haque IS. Expanded carrier screening: A review of early implementation and literature. Semin Perinatol. 2016; 40:29-34.
15. Beauchamp KA, Johansen Taber KA, Muzzey D. Clinical impact and cost-effectiveness of a 176-condition expanded carrier screen. Genet Med. 2019.
16. Martin J, Asan, Yi Y, et al. Comprehensive carrier genetic test using next-generation deoxyribonucleic acid sequencing in infertile couples wishing to conceive through assisted reproductive technology. Fertil Steril. 2015; 104:1286-93.
17. Liberati A, Altman DG, Tetzlaff J, et al. 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.*
(Discusses the methodology for systematic reviews used in the present study)
18. Livingstone J, Axton RA, Gilfillan A, et al. Antenatal screening for cystic fibrosis: a trial of the couple model. BMJ. 1994; 308:1459-62.
19. Brock DJ. Prenatal screening for cystic fibrosis: 5 years' experience reviewed. Lancet. 1996; 347:148-50.
20. Loader S, Caldwell P, Kozyra A, et al. Cystic fibrosis carrier population screening in the primary care setting. Am J Hum Genet. 1996; 59:234-47.
21. Levenkron JC, Loader S, Rowley PT. Carrier screening for cystic fibrosis: test acceptance and one year follow-up. Am J Med Genet. 1997; 73:378-86.

22. Mitchell JJ, Capua A, Clow C, et al. Twenty-year outcome analysis of genetic screening programs for Tay-Sachs and beta-thalassemia disease carriers in high schools. Am J Hum Genet. 1996; 59:793-8.
23. Witt DR, Schaefer C, Hallam P, et al. Cystic fibrosis heterozygote screening in 5,161 pregnant women. Am J Hum Genet. 1996; 58:823-35.
24. Kronn D, Jansen V, Ostrer H. Carrier screening for cystic fibrosis, Gaucher disease, and Tay-Sachs disease in the Ashkenazi Jewish population: the first 1000 cases at New York University Medical Center, New York, NY. Arch Intern Med. 1998; 158:777-81.
25. Lena-Russo D, Badens C, Aubinaud M, et al. Outcome of a school screening programme for carriers of haemoglobin disease. J Med Screen. 2002; 9:67-9.
26. Cronister A, DiMaio M, Mahoney MJ, et al. Fragile X syndrome carrier screening in the prenatal genetic counseling setting. Genet Med. 2005; 7:246-250.
27. Zuckerman S, Lahad A, Shmueli A, et al. Carrier screening for Gaucher disease: lessons for low-penetrance, treatable diseases. JAMA. 2007; 298:1281-90.*
(Compares reproductive choices among couples at risk of having children affected with different sub-types of the same disease)
28. Colah R, Surve R, Wadia M, et al. Carrier screening for beta-thalassemia during pregnancy in India: a 7-year evaluation. Genet Test. 2008; 12:181-5.
29. Christie LM, Ingrey AJ, Turner GM, et al. Outcomes of a cystic fibrosis carrier testing clinic for couples. Med J Aust. 2009; 191:499-501.
30. Massie J, Petrou V, Forbes R, et al. Population-based carrier screening for cystic fibrosis in Victoria: the first three years experience. Aust N Z J Obstet Gynaecol. 2009; 49:484-9.
31. Tongsong T, Charoenkwan P, Sirivatanapa P, et al. Effectiveness of the model for prenatal control of severe thalassemia. Prenat Diagn. 2013; 33:477-83.
32. Franasiak JM, Olcha M, Bergh PA, et al. Expanded carrier screening in an infertile population: how often is clinical decision making affected? Genet Med. 2016; 18:1097-1101.
33. Archibald AD, Smith MJ, Burgess T, et al. Reproductive genetic carrier screening for cystic fibrosis, fragile X syndrome, and spinal muscular atrophy in Australia: outcomes of 12,000 tests. Genet Med. 2018; 20:513-523.**
(Discussed outcomes of a large population-wide carrier screening program for 3 disorders)

34. Ghiossi CE, Goldberg JD, Haque IS, et al. Clinical Utility of Expanded Carrier Screening: Reproductive Behaviors of At-Risk Couples. J Genet Couns. 2018; 27:616-625.
35. Mathijssen IB, Holtkamp KCA, Ottenheim CPE, et al. Preconception carrier screening for multiple disorders: evaluation of a screening offer in a Dutch founder population. Eur J Hum Genet. 2018; 26:166-175.
36. Taber KAJ, Beauchamp KA, Lazarin GA, et al. Clinical utility of expanded carrier screening: results-guided actionability and outcomes. Genet Med. 2019; 21:1041-1048.**
(The largest ECS-based study to date, reviewing reproductive outcomes of ARCs)
37. Chokoshvili D, Vears DF, Borry P. Reproductive autonomy in expanded carrier screening: more than meets the eye? Expert Rev Mol Diagn. 2018; 18:993-994.
38. Myring J, Beckett W, Jassi R, et al. Shock, adjust, decide: reproductive decision making in cystic fibrosis (CF) carrier couples--a qualitative study. J Genet Couns. 2011; 20:404-17.
39. Ioannou L, Delatycki MB, Massie J, et al. "Suddenly Having two Positive People who are Carriers is a Whole New Thing" - Experiences of Couples Both Identified as Carriers of Cystic Fibrosis Through a Population-Based Carrier Screening Program in Australia. J Genet Couns. 2015; 24:987-1000.
40. Zuckerman S, Lahad A, Zimran A, et al. Attitudes of couples identified through screening as carriers of Gaucher disease type 1. Clin Genet. 2008; 74:566-70.
41. Chokoshvili D, Borry P, Vears DF. A systematic analysis of online marketing materials used by providers of expanded carrier screening. Genet Med. 2018; 20:976-984.
42. Chokoshvili D, Van Steijvoort E, Borry P. Ethical challenges in offering expanded carrier screening in the context of third-party reproduction. Médecine de la Reproduction, Gynécologie et Endocrinologie. 2019.
43. Mertes H, Lindheim SR, Pennings G. Ethical quandaries around expanded carrier screening in third-party reproduction. Fertil Steril. 2018; 109:190-194.
44. Scotet V, Dugueperoux I, Audrezet MP, et al. Prenatal diagnosis of cystic fibrosis: the 18-year experience of Brittany (western France). Prenat Diagn. 2008; 28:197-202.