

Reproductive genetics

An ESHG–ESHRE survey on the current practice of expanded carrier screening in medically assisted reproduction

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ABSTRACT

STUDY QUESTION: What is the current practice and views on (expanded) carrier screening ((E)CS) among healthcare professionals in medically assisted reproductive (MAR) practices in Europe?

SUMMARY ANSWER: The findings show a limited support for ECS with less than half of the respondents affiliated to centres offering ECS, and substantial variation in practice between centres in Europe.

WHAT IS KNOWN ALREADY: The availability of next-generation sequencing, which enables testing for large groups of genes simultaneously, has facilitated the introduction and expansion of ECS strategies, currently offered particularly in the private sector in the context of assisted reproduction.

STUDY DESIGN, SIZE, DURATION: A cross-sectional survey evaluating practice and current views among professionals working in MAR practice in different European countries was designed using the online SurveyMonkey tool. The web-based questionnaire included questions on general information regarding the current practice of (E)CS in MAR and questions on what is offered, to whom the test is offered, and how it is offered. It consisted mostly of multiple-choice questions with comment boxes, but also included open questions on the respondents' attitudes/concerns relevant to (E)CS practice, and room to upload requested files (e.g. guidelines and gene panels). In total, 338 responses were collected from 8 February 2022 to 11 April 2022.

PARTICIPANTS/MATERIALS, SETTING, METHODS: The online survey was launched with an invitation email from the ESHRE central office (n = 4889 emails delivered) and the European Society of Human Genetics (ESHG) central office (n = 1790 emails delivered) sent to the ESHRE and ESHG members, and by social media posts. The survey was addressed to European MAR centres or gamete banks and to centres located in non-European countries participating in the European IVF-monitoring Consortium. Two reminder emails were sent. After exclusion of 39 incomplete responses received (e.g. only background information), 299 respondents from 40 different countries were included for analyses.

MAIN RESULTS AND THE ROLE OF CHANCE: Overall, 42.5% (127/299) of respondents were affiliated to centres offering ECS. The perceived responsibility to enable prospective parents to make informed reproductive decisions and preventing suffering/burden for parents were the main reasons to offer ECS. A single ECS panel is offered by nearly 45% (39/87 received answers) of the centres offering ECS, 25.3% (22/87) of those centres offer a selection of ECS panels, and 29.9% (26/87) offer whole exome sequencing and a large in silico panel. Different ranges of panel sizes and conditions were included in the ECS panel(s) offered. Most of the respondents (81.8%;

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72/88 received answers) indicated that the panels they offer are universal and target the entire population. Pathogenic variants (89.7%; 70/78 received answers), and to a lesser extent, likely pathogenic variants (64.1%; 50/78 received answers), were included in the ECS report for individuals and couples undergoing MAR with their own gametes. According to 87.9% (80/91 received answers) of the respondents, patients have to pay to undergo an ECS test. Most respondents (76.2%; 61/80 received answers) reported that counselling is provided before and after the ECS test. Preimplantation genetic testing, the use of donor gametes, and prenatal diagnostic testing were the three main reproductive options discussed with identified carrier couples. The main reason, according to the respondents, for not offering ECS in their centre, was the lack of professional recommendations supporting ECS (52.5%; 73/139 received answers) and the high cost for couples or reimbursement not being available (49.6%; 69/139). The challenges and moral dilemmas encountered by the respondents revolved mainly around the content of the offer, including the variants classification and the heterogeneity of the panels, the counselling, and the cost of the test.

LIMITATIONS, REASONS FOR CAUTION: Although the total number of respondents was acceptable, the completion rate of the survey was suboptimal. In addition, the heterogeneity of answers to open-ended questions and the ambiguity of some of the answers, along with incomplete responses, posed a challenge in interpreting survey results. It is also plausible that some questions were not easily understood by the respondents. For this reason, response and non-response bias are acknowledged as further limitations of the survey.

WIDER IMPLICATIONS OF THE FINDINGS: The results of this survey could aid in identifying potential challenges or areas for improvement in the current practice of ECS in the MAR field and contribute to the discussion on how to address them. The results underline the need to stimulate a more knowledge-based debate on the complexity and the pros and cons of a possible implementation of ECS in MAR.

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Keywords: carrier screening / assisted reproduction / genetic testing / inherited disease / genetic disorder / congenital abnormalities

Introduction

Overall, ~1–2% of couples in the general population face an increased risk of having a child affected by a serious recessive genetic disorder, regardless of family history or ethnicity (Lazarin *et al.*, 2013; Chokoshvili *et al.*, 2018b; Capalbo *et al.*, 2019). In specific situations, such as consanguinity or among certain ethnic groups with a high inbreeding coefficient, this risk is elevated either for all recessive diseases or specifically increased for a few conditions because of the founder effect (Hamamy *et al.*, 2011; Oniya *et al.*, 2019).

Carrier screening aims to detect asymptomatic carriers of recessive disorders, autosomal or X-linked, to provide them with information on their reproductive genetic risk, and relative reproductive options (Human Genetics Commission, 2011; Dondorp *et al.*, 2014; Henneman *et al.*, 2016; ACOG, 2017; Delatycki *et al.*, 2020).

For conditions that are relatively common in a specific population or group, carrier screening may be offered at population level, and not necessarily managed by specialized clinical genetic services.

Population carrier screening has been performed for over 50 years, evolving significantly since the establishment of the first carrier screening programmes for sickle cell disease in 1966 (Antonarakis, 2019). Initially limited to populations with a higher risk based on ancestry, early programmes targeted diseases such as Tay-Sachs disease for the Ashkenazi Jewish population (Kaback, 2000) and haemoglobinopathies for individuals from Mediterranean regions (Cousens *et al.*, 2010). At that time, screening primarily involved biochemical or haematological tests, reducing the frequency of affected live births (Kaback, 2000; Cao, 2002; Cousens *et al.*, 2010; Canatan, 2014; Canatan *et al.*, 2021). As DNA testing became possible, carrier screening based on molecular methods was introduced, with cystic fibrosis (CF) being one of the early conditions considered (Bell *et al.*, 2011).

Recent advancements in genomic sequencing technologies and the discovery of thousands of disease-associated genes have given rise to new screening approach: expanded carrier screening (ECS). ECS involves testing a large number of autosomal recessive and X-linked genetic disorders, usually utilizing high-throughput sequencing platforms. It has the potentiality to identify more carriers across all ethnicities, earning it the label of universal carrier screening (Lazarin *et al.*, 2013; Haque *et al.*, 2016; Guo and Gregg, 2019; Dolitsky *et al.*, 2020; Westemeyer *et al.*, 2020). Since the introduction of the first ECS panels, the number of genes and pathogenic variants included has increased significantly, ranging from tens to hundreds (Chokoshvili *et al.*, 2017). As a result, both the quantity and the selection of the conditions have varied widely (Chokoshvili *et al.*, 2018a,b; Rowe and Wright, 2020). Methodologies also range from the focused targeting of selected pathogenic variants, to full-gene sequencing of a specific panel of genes, known as an ‘in silico gene panel’ (Antonarakis, 2019). Despite recommendations from scientific societies outlining basic principles for ECS gene panel development over the years (Grody *et al.*, 2013; Edwards *et al.*, 2015; Henneman *et al.*, 2016; ACOG, 2017), significant heterogeneity and inconsistency still persist in clinical application (Chokoshvili *et al.*, 2018a, Kraft *et al.*, 2019). Main concerns revolve around ECS panel design, including conditions with questionable clinical utility (Guo and Gregg, 2019; Balzotti *et al.*, 2020; Kirk *et al.*, 2021), clinical management, reporting strategies (individual- or couple-based disclosure) (Capalbo *et al.*, 2019), pre- and post-counselling requirements, and addressing psychological and financial considerations, as well as the overall proportionality of this strategy (Sparks, 2020; de Wert *et al.*, 2021; Shapiro *et al.*, 2021; van Dijke *et al.*, 2021).

Furthermore, despite being a potentially beneficial strategy (Busnelli *et al.*, 2023), ECS has not gained widespread adoption in many places, and its application has primarily been confined to the practice of IVF, particularly in the USA, where ECS seamlessly

integrates into the routine pre-treatment work-up for patients (Ramdaney et al., 2022). Although infertility itself is not a risk factor for recessive genetic diseases, and IVF patients are not necessarily at greater risk compared to the general population, infertile individuals already undergo a highly medicalized reproductive process, making the inclusion of an additional test possibly less impactful. Moreover, couples seeking infertility treatments often appreciate additional information about their reproductive risks, and in the event of an identified increased genetic risk, a modification to their reproductive treatment may be possible, such as preimplantation genetic testing (PGT) for monogenic diseases.

While some couples undergoing medically assisted reproduction (MAR) have benefited from ECS by being identified as carriers enabling reproductive choice (Capalbo et al., 2021; Wyns et al., 2022), it is less obvious what the current repercussions on the local healthcare systems are in relation to counselling for the couples or their relatives, particularly when the partner carrier testing would not be offered, or whether this strategy can enable cascade testing in those families. Furthermore, recent studies have also investigated the application of carrier screening of gamete donors, investigated existing regulations, and determined that great variability exists in this practice as well. Concerns are associated with, among others, the protection of privacy and autonomy interests of gamete donors, and a possible rejection of a greater number of gamete donors (Dondorp et al., 2014; Pennings, 2020; Payne et al., 2021; Pennings et al., 2021) without considering the possibility to perform a recipient matching.

Therefore, it remains unclear how ECS is implemented in MAR centres and gamete banks, and what practices are being employed. The aim of the present study is to acquire data to support the current discussion and inform future recommendations regarding ECS, particularly in relation to MAR.

We specifically investigated professional experiences and opinions on issues surrounding ECS, irrespective of ECS experience, along with the technical aspects relevant to offering ECS, and strategies of clinical management. The ultimate goal was to identify potential challenges or areas for improvement of the ECS practice in MAR centres.

Materials and methods

Study design

This is a cross-sectional survey conducted using an online structured questionnaire on reproductive ECS. The questionnaire was developed in English by a multidisciplinary working group including members from ESHRE and the European Society of Human Genetics (ESHG) (Supplementary Data File S1). This survey was anonymous and is exempt from ethics review.

Questionnaire

The questionnaire included an introduction explaining carrier screening and inviting centres offering or not offering (E)CS to complete the survey, with a first section on general information regarding the current practice of (E)CS in the MAR field and two sections specific to those centres offering (E)CS: one section was addressed to centres offering (E)CS for couples/individuals using their own gametes and the other section was addressed to centres offering (E)CS for gamete donors. Questions on what is offered at the centre, to whom the test is offered, and how it is offered were asked and were mostly multiple-choice questions with comment boxes. The survey also included open questions on the respondents' attitudes/concerns relevant to (E)CS practice, in addition to room to optionally upload some requested

files (e.g. guidelines and gene panels). The complete questionnaire can be found in [Supplementary Data File S2](#).

Participant recruitment

The online survey was launched via SurveyMonkey on 8 February 2022 with an invitation email from the ESHRE central office (n=4889 emails delivered) and the ESHG central office (n=1790 emails delivered) sent to the ESHRE and ESHG members, and by social media posts. The survey was addressed to professionals working at European MAR centres or gamete banks and to centres located in non-European countries participating in the European IVF-monitoring Consortium, notably Armenia and Kazakhstan. Two reminder emails were sent. The survey was closed after 2 months on 11 April 2022.

Data analysis

Statistical analysis was performed using IBM Statistical Package software SPSS version 28.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were computed for all items and categorical data were reported as frequencies and percentages. Incomplete responses with only background information (i.e. only information on the country or profession) were not considered. Duplicate responses (respondents being affiliated to the same centre) could not be detected because identifying parameters were not collected. However, it was stated in the introduction of the survey that the questionnaire should be completed by only one representative of each centre. Some respondents dropped out before completing all the survey questions, and some questions were answered by only a few of the respondents. The percentages and frequencies were calculated according to the number of answers received for each single question.

Results

Responses

In total, 338 replies were received. After exclusion of 39 incomplete responses (e.g. only background information), 299 respondents from 40 different countries were included for analyses. The largest number of respondents were affiliated to centres from Spain (n=35) followed by the UK (n=28) and Italy (n=23) (Fig. 1A). Most respondents (64.9%; 194/299) indicated that they were affiliated to either private (37.5%; 112/299) or public (27.4%; 82/299) MAR centres and most were either embryologists (25.1%; 75/299), MAR clinicians/gynaecologist (25%; 75/299), or clinical geneticists (23.1%; 69/299) (Fig. 1B and C).

Carrier screening/testing offered

The participants were asked about the type of genetic carrier tests offered in their centre, with multiple response options provided. A minority (4.0%; 12/299) offered no carrier testing. Carrier testing for specific conditions (e.g. CF, spinal muscular atrophy, fragile X syndrome) was reported most frequently, being offered by 65.8% (197/299) of the centres. Other options included screening/testing for a selected small panel of frequent diseases (<10 diseases) (30.4%; 91/299), a selected number of genes with a targeted sequencing approach (28.4%; 85/299), or whole exome sequencing (WES) (24.4%; 73/299) (Fig. 2). A minority of centres (2.7%, 8/299) offer all the different types of carrier testing mentioned above.

Offering ECS

In total, 127/299 (42.5%) respondents reported that they were affiliated to centres that offered some kind of ECS, performing either in-house testing (27.6%, 35/127), or outsourcing (72.4%, 92/

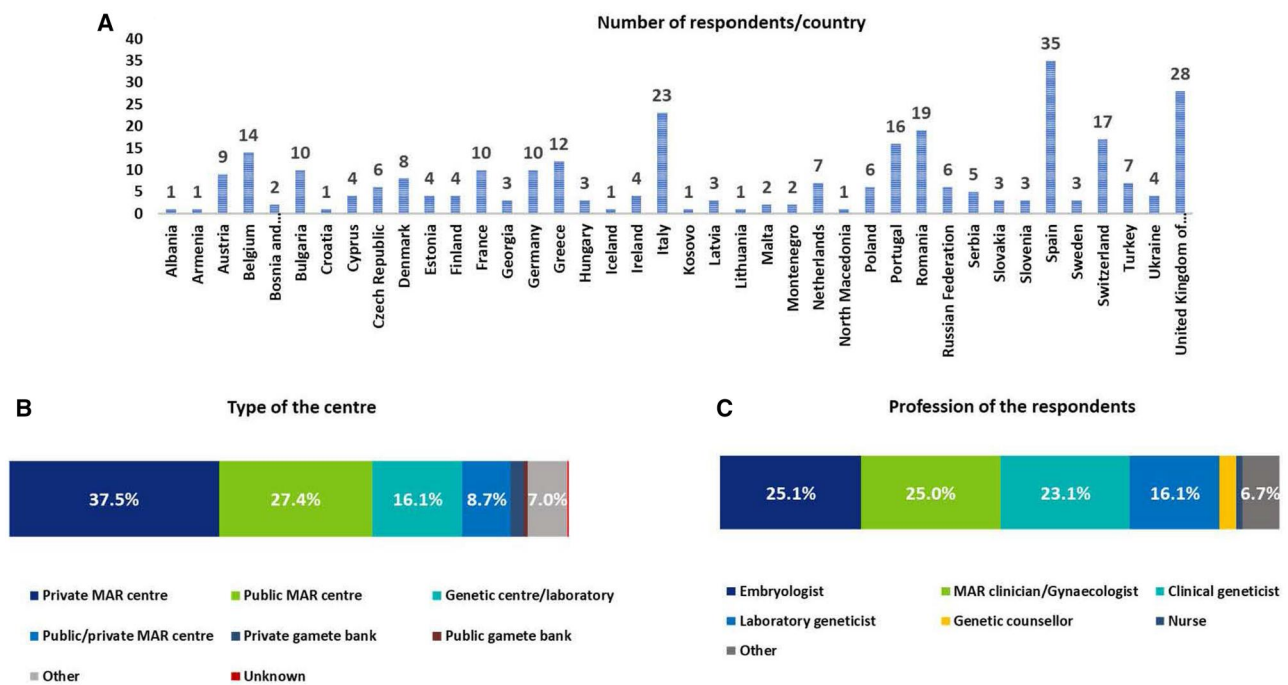


Figure 1. Characteristics of centres and respondents by country, centre type, and profession. Characteristics of the 229 respondents, including country (Panel A), type of centre (Panel B), and the profession of the respondent (Panel C). The countries are listed by alphabetical order. MAR, medically assisted reproduction.

Genetic testing offered to patients in 299 centres

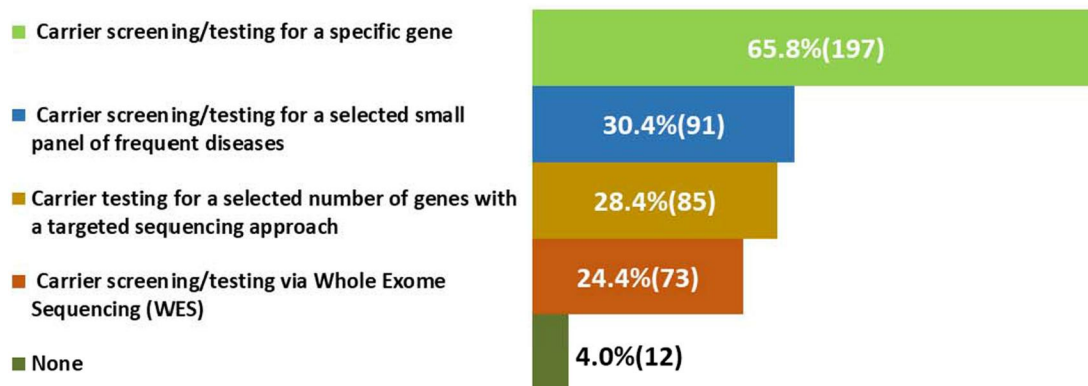


Figure 2. Type of carrier screening/testing offered by participating centres. Percentage of respondents representing centres offering each test is indicated.

127) (Fig. 3A). Most centres (70.1%; 89/127) that offer ECS also offered some type of PGT (Supplementary Table S1).

Based on responses from 91/127 respondents affiliated to centres offering ECS, the profiles of tested (MAR) couples/individuals were diverse. The respondents were able to choose more than one option. Carrier screening was mostly offered to couples requesting the test (67.0%; 61/91), couples with family history (64.8%; 59/91), or consanguineous couples (53.8%; 49/91) (Fig. 3C). Of those 127 respondents, 85 answered the question if their centre offered ECS to gamete donors and 62.4% (53/85) of those respondents confirmed such testing was offered in their centre (Fig. 3D).

Of all 172 respondents who mentioned that their centres did not offer ECS (Fig. 3A), 15.1% (26/172) were considering offering ECS in the future, with a time scale varying from a few months to 2–3 years, and 22.7% (39/172) did not consider offering ECS in the

future (Fig. 3B). A large percentage declared themselves as 'unsure' (41.3%; 71/172) or did not respond (20.9%; 36/172).

Reasons for offering/not offering ECS

Respondents' agreement on reasons for (not) offering is shown in Tables 1 and 2. Most agreed on the importance of supporting informed reproductive decisions (85.7%; 78/91), preventing suffering/burden (81.3%; 74/91), and identifying couples at-risk (79.1%; 72/91). Agreement on other reasons are listed in Table 1.

However, there was not a strong agreement among respondents regarding the rationale behind not offering RCS. The main reasons were lack of supporting professional recommendations (52.5%; 73/139), high cost (49.6%; 69/139), and unclear benefit (37.4%; 52/139). One-fourth of respondents attributed their centres non-offering of ECS to the perceived 'Low prevalence/low risk of recessive disorders' (24.5%; 34/139) (Table 2).

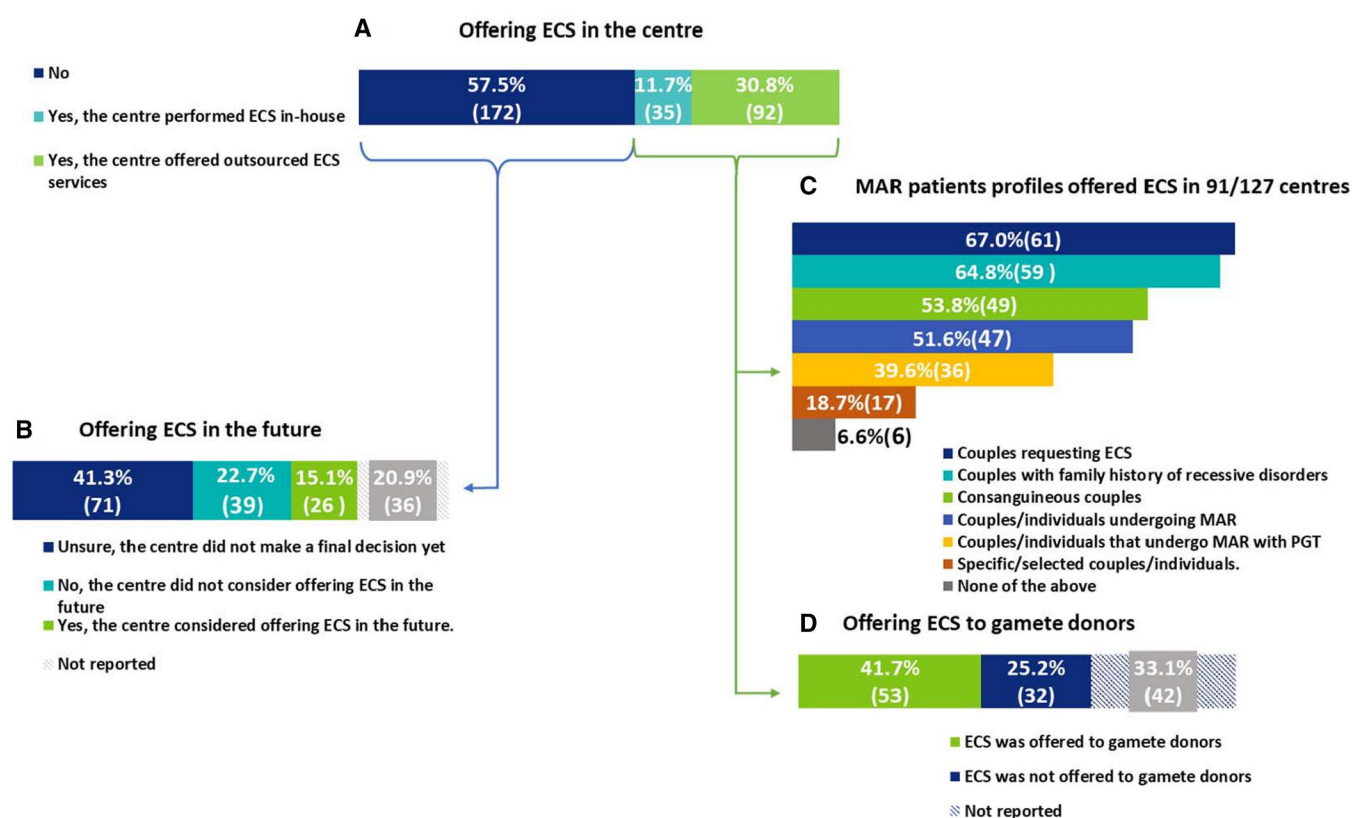


Figure 3. Offering expanded carrier screening. Number of centres in Europe offering or not offering ECS, with percentages based on the total number of responses received ($n = 299$) (A). Centres considering or not offering ECS in the future ($n = 172$) (B). The profiles of MAR patients offered ECS ($n = 91$) (C). Centres offering or not ECS to gamete donors, with percentages based on the total number of centres offering ECS ($n = 127$) (D). Not reported correspond to missing answers. ECS, expanded carrier screening; MAR, medically assisted reproduction; PGT, preimplantation genetic screening.

Table 1. Reasons for offering expanded carrier screening.

	N/A (%)	(Strongly) Disagree (%)	Neutral (%)	(Strongly) Agree (%)
To enable prospective parents to make informed reproductive decisions	2.2	3.3	8.8	85.7
To prevent suffering/burden for parents	2.2	5.5	11.0	81.3
To identify patients with a high risk of an affected pregnancy	4.4	8.8	7.7	79.1
To help avoid high costs of health care for children affected with conditions	3.3	14.3	26.4	56.0
To take account of the welfare of the intended child	6.6	11.0	29.7	52.7
Because patients ask for extra tests	2.2	32.9	26.4	38.5
Because other clinics/banks are offering it	4.4	42.8	31.9	20.9
For research purposes	15.4	46.2	23.1	15.4

Results are represented as percentages. $n = 91$ answers received/127 respondents from European centres offering expanded carrier screening. N/A, not applicable.

Recommendations from professional societies regarding the application of ECS

In total, 45.8% (137/299) of the respondents indicated that there are no recommendations in their country regarding the application of ECS. Additionally, 16.7% (50/299) reported that there are no country-specific recommendations, but they consider international recommendations, e.g. from the ESHG (Henneman et al., 2016), ESHRE (de Wert et al., 2021), and the American College of Obstetrics and Gynaecology (ACOG, 2017). 19.7% (59/299) considered recommendations from national professional societies while 17.7% (53/299) of the respondents indicated that they did not know whether or not there are recommendations in their country. Supplementary Table S2 provides national

recommendations and advisory reports regarding the (E)CS provided by respondents from four countries.

More than the half of the respondents from centres not offering ECS (59.3%; 102/172) reported that there are no recommendations from professional societies in their countries (Table 3).

One question in the survey aimed to assess the attitude of the respondents towards the recommendations from the international societies (ESHG, Henneman et al., 2016; ESHRE, de Wert et al., 2021) to focus only on serious early-onset recessive conditions. Most (80.0%; 72/90) of the respondents who answered this question agreed with the statement of the international societies' recommendations, while 6.7% (6/90) did not agree (because of the difficulty to define a serious early-onset recessive condition)

Table 2. Reasons for not offering expanded carrier screening.

	N/A (%)	(Strongly) Disagree (%)	Neutral (%)	(Strongly) Agree (%)
Lack of professional recommendations supporting ECS	17.2	12.9	17.3	52.5
Due to high cost for couples or reimbursement being not available	20.1	12.9	17.3	49.6
Unclear benefit of the test	18.0	24.5	20.1	37.4
The centre had other priorities	24.5	23.0	20.1	32.4
Low prevalence/low risk of recessive disorders	22.3	34.5	18.7	24.5
Lack of knowledge/skills to offer ECS	21.6	33.8	18.7	22.3
Legal restrictions	21.6	36.0	20.1	22.3
Due to high costs for our centre and/or to workload and lack of time	24.8	29.2	24.1	22.0
The centre did not want to burden the patients with difficult decisions on ECS (results)	56.1	13.7	12.2	18.0
Unfamiliar with ECS	67.6	13.7	7.9	10.8

Results are represented as percentages. n = 139 answers received from 172 respondents from centres not offering ECS. ECS, expanded carrier screening; N/A, not applicable.

Table 3. Correlation between offering expanded carrier screening and considering guidelines from professional societies.

		Are there any recommendations from professional societies in your country regarding the application of expanded carrier screening? n (%)				
		Yes	No	No, but we consider international recommendations	I don't know	Total
Do you, in your centre, offer ECS?	No	20 (11.6%)	102 (59.3%)	17 (9.9%)	33 (19.2%)	172
	Yes, we perform ECS in-house	16 (45.7%)	5 (14.3%)	8 (22.9%)	6 (17.1%)	35
	Yes, we perform outsourced ECS services	23 (25.0%)	30 (32.6%)	25 (27.2%)	14 (15.2%)	92
	Total	59	137	50	53	299

Results are represented as actual numbers of respondents and corresponding percentages. ECS, expanded carrier screening.

and 13.3% (12/90) were not aware of these recommendations (Table 3).

ECS test/panel offered

Out of 127 respondents who indicated that their centre provided ECS, 87 (68.5%) respondents provided additional details about the tests. Among these, 44.8% (39/87) mentioned their centres offered a single ECS panel, while 25.3% (22/87) provided a selection of ECS panels. The remaining 29.9% (26/87) offered WES and a large virtual panel. Panels included up to 500 genes (40 respondents), up to 1200 genes (8 respondents) or more (up to 2000 genes) (8 respondents).

The range of conditions included in the ECS panel consisted of autosomal recessive disorders (92.3%; 84/91 responses received), X-linked disorders (85.7%; 78/91), late-onset dominant disorders (18.7%, 17/91), and dominant disorders only when a recessive form also exists (e.g. BRCA2) (1.1%; 1/91). However, 3.3% (3/91) of the respondents were uncertain about specific conditions included in the ECS panel(s). Among the respondents who stated including late-onset dominant disorders in their ECS panel, none provided details of these disorders, or a clear explanation of the criteria used for this wider selection.

Respondents indicated that panels were targeting the whole population (universal offer) (81.8%; 72/88 received answers) or adapted to high-risk groups based on consanguinity, ancestry ethnicity, and/or family history (18.2%; 16/88 received answers).

Individual- or couple-based ECS, and information included in the ECS report

Out of 127 respondents affiliated to centres offering ECS, 78 (61.4%) provided answers regarding whom to test. In cases where

a couple used their own gametes, the centres recommended simultaneous screening for both partners (57.7%; 45/78) or sequential screening for partners (25.6%; 20/78) (Fig. 4A). The respondents disclosed different types of information and genetic variants were included in the reports; pathogenic variants (89.7%; 70/78 received answers), likely pathogenic variants (64.1%; 50/78 received answers) and variants of unknown significance (VUS) (16.7%; 13/78 received answers) (Fig. 4B–D).

Cost of ECS test

Most respondents (87.9%; 80/91 received responses) indicated that patients have to pay to undergo an ECS test, while only 11.0% (10/91) of those answering this question—representing public MAR centres from various countries and one gamete bank—indicated that there is no cost for the patient and ECS is reimbursed.

Different prices were given by the respondents depending on what is offered and on the country. For a single ECS panel, most prices were reported to vary between €150 and €800. For the centres offering a selection of ECS panels, prices vary between €150 and €1800. For the WES, prices given varied between €400 and €2500.

Informed consent and pre- and/or post-test counselling

Informed consent was a prerequisite for the majority of the respondents (Fig. 5A). Based on 80 responses received about counselling of tested MAR couples/individuals undergoing MAR with their own gametes, only 2.5% (2/80) of the centres did not offer counselling about ECS. Regarding gamete donors, 11.3% (6/53) of respondents did not provide counselling. The majority of

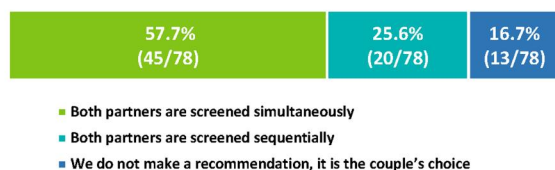
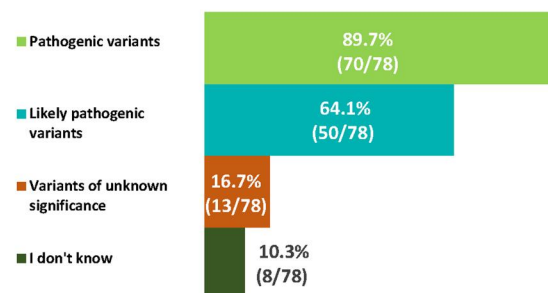
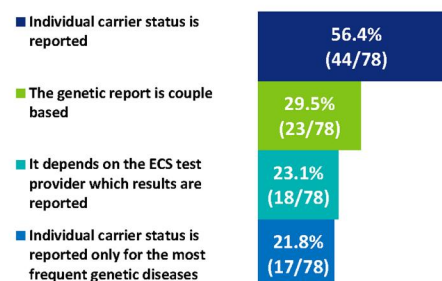
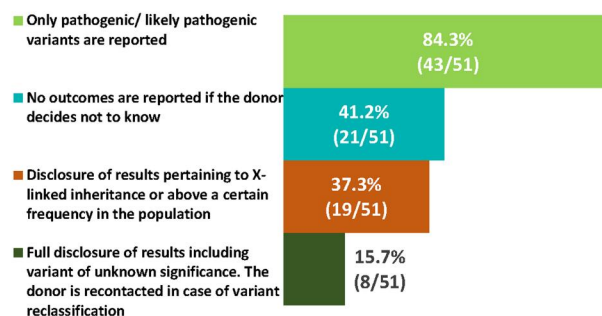
A Simultaneous or sequential couple screening**C Genetic variants reported in the ECS reported to couples/individuals undergoing ART with their own gametes****B Information included in the ECS report of couples/individuals undergoing MAR with their own gametes****D Outcomes of ECS testing reported to the gamete donor**

Figure 4. Couple screening and results reporting strategies. Couples can be screened simultaneously or sequentially (A). Information included in the ECS report and different strategies for results reporting in the case of couple undergoing MAR with own gametes (B and C) or gamete donor (D) screening, ECS, expanded carrier screening.

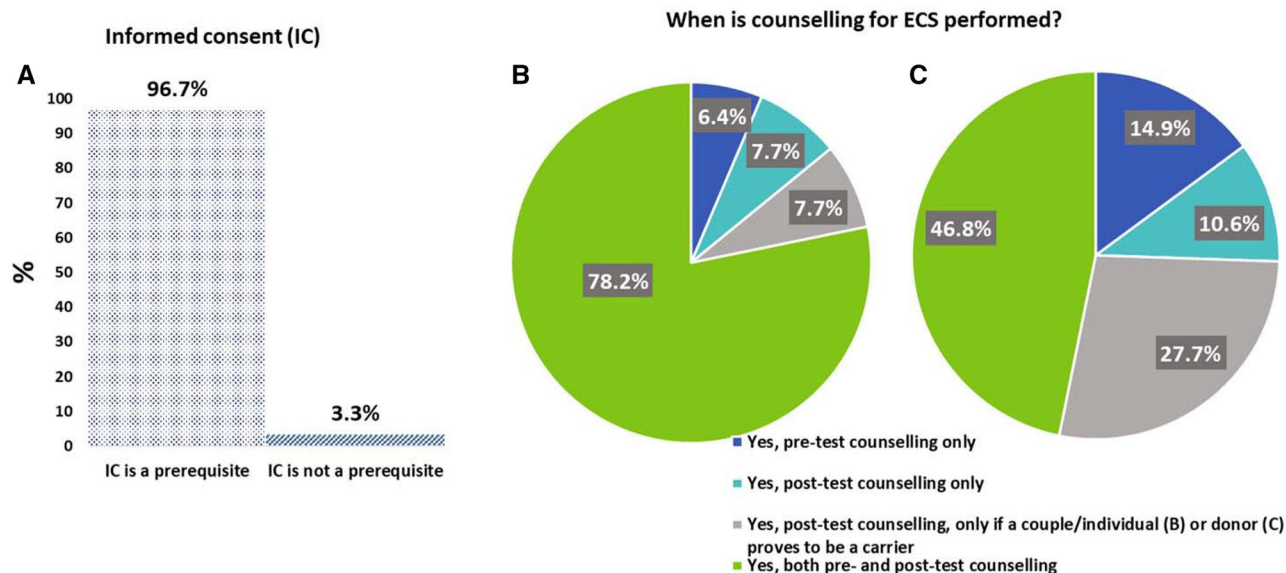


Figure 5. Informed consent and pre- and/or post-test counselling. Prerequisite of informed consent (n = 80) (A) and time of counselling for couples/individuals (n = 78) (B) and gamete donors (n = 47) (C) undergoing ECS. ECS, expanded carrier screening.

respondents indicated that counselling was offered pre- and post-test (Fig. 5B and C).

In 43.6% (34/78) of the cases where counselling was offered to tested couples/individuals undergoing MAR with their own gametes, counselling was performed primarily by the clinical geneticist, and otherwise by a reproductive specialist, genetic counsellor, or other staff, depending on time of the counselling (pre- or post-test counselling) and test result (negative or

positive). Similar answers were given when counselling was offered to tested gamete donors (data not shown).

Policy of the centre on reproductive options after ascertaining carrier status

The question about reproductive preventative options in case a carrier couple is at high risk of having a child with a severe inherited disease, was answered by 63.0% (80/127) of respondents. The

indicated options discussed with the couple included PGT (92.5%; 74/80), use of donor gametes (78.8%; 63/80), prenatal diagnostic testing (72.5%; 58/80), adoption (36.3%; 29/80), conceiving a child and accept the risk/consequences (33.8%; 27/80), and refraining from having a(nother) child (21.3%; 17/80). Only 10% (8/80) of the respondents indicated that they discuss all the above reproductive options with the carrier couple.

Nearly half of respondents (47.8%) indicated that access to MAR was provided only on the condition that the identified carrier couple was willing to make use of the preventative measures discussed.

In case a gamete donor was identified as being a carrier in ECS testing, 69.6% (32/46) of the centres matched the carrier donor by testing the recipient (ECS or specific gene), 19.6% (9/46) of the centres did not use the carrier donor for reproductive donation, and 10.9% (5/46) excluded only donors that were carriers for the most frequent conditions.

Based on the answers of 75 respondents, the disease indication (85.3%; 64/75) and the national regulation (64%; 48/75) were two main reported factors to consider when recommending a reproductive option to a carrier couple/individual. Also, the situation of the couple/individual and the treatment they intend to have (e.g. whether they were already undergoing PGT) were taken into consideration by 61.3% (46/75) of respondents.

Challenges and issues of ECS

The question about whether the respondents encountered challenges or moral dilemmas or wanted to communicate issues and lessons learned regarding offering ECS was answered by 27 respondents. Most answers can be subsumed under the headings of content of a possible offer, consequences, counselling, and cost. Regarding the content, for instance, uncertainties owing to variable penetrance and variant classification, as well as heterogeneity of panels and inclusion of, e.g. milder variants were mentioned. Dilemmas pertaining to consequences of ECS related, e.g. to lack of availability of termination of pregnancy or PGT. Challenges to counselling were mentioned in relation, e.g. to difficulties in interpretation. Costs were mentioned as a barrier and sometimes ECS was only offered in a research setting.

Discussion

This survey aimed to investigate the perspectives of health professionals and current use of ECS in MAR practices in Europe. The findings show that less than half of the respondents were affiliated to centres offering ECS, while large heterogeneity was found regarding how ECS was offered in these centres. The main reason for offering ECS reported by respondents was to enable prospective parents to make informed reproductive decisions, prevent suffering/burden for parents, and to identify those parents with a high risk for a child with a genetic disorder. The most common reproductive options offered to carrier couples reported included PGT, the use of donor gametes, and prenatal diagnostic testing in line with earlier reported couples' choices (Cannon *et al.*, 2019). Main reason not to offer ECS was a lack of professional recommendations supporting ECS, the high cost for couples or reimbursement being not available, and unclear benefit of the test.

It has been argued that reproductive genetic screening could be of particular interest for those individuals seeking IVF or other forms of MAR, considering the highly medicalized process they are undergoing for achieving a pregnancy and the wide range of reproductive options available to them (Cho *et al.*, 2013; Franasiak *et al.*, 2016; de Wert *et al.*, 2021). However, as slightly

over half of the respondents indicate their centre does not offer ECS, and about one-third are not, or are unsure about, planning to offer it in the future, this survey seems to indicate there is currently no general willingness to offer ECS in MAR practices in Europe, which may be related to respondents' perceived barriers to offer such screening, as previously shown (Klein *et al.*, 2024).

In our study, respondents commonly cited the absence of professional recommendations endorsing ECS as the primary reason for not offering it, suggesting a structural barrier (Holtkamp *et al.*, 2017). The limited presence of national recommendations and the low awareness of available international guidelines underscore the need for improved dissemination strategies for existing guidance.

The unclear benefit of the test was also reported as a reason for not offering ECS. A literature review has shown that most couples chose carrier screening to prevent the birth of an affected child (Cannon *et al.*, 2019). Additionally, the vast majority of identified at-risk couples pursue actions primarily involving PGT and prenatal diagnosis to prevent the birth of affected offspring. Therefore, while the objectives of ECS and its potential beneficial effects are well established, some responses may stem from a lack of proper knowledge regarding the fundamentals of carrier screening.

In a recent paper, ESHRE concluded that, given the many questions still unanswered on the benefits of ECS in MAR practices, similar to the challenges and issues identified in our study, the proportionality of ECS in applicants of MAR has not yet been substantiated and that centres that have implemented or consider implementing such ECS have the responsibility to embed such ECS in (multidisciplinary) research, aimed at gathering relevant data (de Wert *et al.*, 2021). We consider this still to be the most important professional guidance for the time being.

Several clusters of issues regarding the introduction of ECS to prospective parents applying for MAR can be identified from our results, reflecting questions on whether and how to offer ECS. Following the principle that any (offer of) screening should meet the 'ethical criteria' of proportionality, respect for autonomy, and justice, we will discuss the findings under these headings to allow for identifying knowledge gaps and weighing the potential benefits and harms of offering ECS.

Regarding proportionality, the pros and cons of differences regarding how ECS is offered become apparent. A literature review of panels offered by (commercial) providers showed a large variety and range of conditions being included in panels, with only three conditions screened for by all providers (Maple syrup urine disease type 1B, CF and other CFTR-related disorders, and Niemann–Pick disease A/B) (Chokoshvili *et al.*, 2018b). In the current survey, those respondents reporting their centre to offer ECS indicated this is done either by targeted panel testing or WES. The reported panels were of three general sizes, namely 40–500 genes, 500–1200 genes, and 1200–2000 genes. Except for consanguineous couples, this approach of screening for large numbers of genes seems to be objectively in contrast to what is recommended by scientific societies and, in general, not supported by the available evidence and knowledge in the field of clinical genetics (Capalbo *et al.*, 2019; Guo and Gregg, 2019; Sallevelt *et al.*, 2021). Adding genes above a certain carrier rate threshold, which corresponds to a predetermined level of carrier frequency within a population, is known to increase complexity of interpretation, lowering accuracy of the screening approach without substantial gains in terms of sensitivity and diagnostic yield, with some exception (i.e. consanguineous couple).

In addition to autosomal and X-linked recessive disorders, 18.7% of the respondents reported offering screening for adult-onset dominant disorders. This practice is not in line with the ESHG, ESHRE, or any other recommendation in the ECS field, which suggest to focus, at least for the time being, on severe recessive, congenital, and childhood disorders (Henneman et al., 2016; de Wert et al., 2021). As presymptomatic testing for later-onset autosomal dominant disorders informs people about their personal risk for future disorders, a blurring of carrier screening and pre-symptomatic testing for late(r)-onset conditions further complicates genetic counselling—and needs further scrutiny. The practice of ECS does not exclude the risk of transmitting a recessive disease. Indeed, for recessive diseases, this will depend on the list of genes tested and the type of tests proposed (assay sensitivity): sequencing with detection of all the known variants of the genes analysed, or detection of the most common variants. For dominant pathologies, which should not be tested, the transmission of pathogenic variants in dominant genes or the occurrence of a *de novo* mutation cannot be ruled out because this is obviously outside the scope of ECS. In all cases, couples should be informed of the residual risks and the screening objectives. A partial explanation of this unexpected finding could stem from the poor understanding of some respondents because no evidence was obtained that autosomal dominant conditions are present in the ECS gene-panel lists provided by the respondents.

We also found variety in respondents' answers on the approach to couple screening and genetic variant reporting. While 57.7% (45/78) of respondents who answered the question on whom to test mentioned their centre recommends testing for both partners, including couples who are consanguineous, 25.6% (20/78) indicated their centre recommends screening both partners sequentially (after the first partner tests positive). Testing both partners simultaneously would be less time-consuming and avoid the challenge of arranging a second clinic visit to collect the partner's sample and to process the genetic test. An alternative strategy for screening couples is to collect both partners' samples in tandem, but testing the second partner's sample only if the first partner was found to be a carrier of an autosomal recessive condition (Arjunan et al., 2021). Given the evolution of the ECS with the inclusion of a greater number of pathologies, and insofar as most individuals are carriers of at least one pathogenic variant, it seems more rational to opt for a couple-based screening approach. Testing both partners allows for better communication of residual risks in a shorter timeframe.

With regard to the information included in the ECS report, 16.7% (13/78) stated that they include VUS in their report. This is worrisome, as guidelines stress that VUS, with very few exceptions, should not be reported (Deans et al., 2022), and especially not in the context of reproductive decision making. ESHG and ESHRE have recommended that the main focus of an ECS report should be on genetic variants that have a clear impact on function in order to avoid psychological stress and decision-making problems linked with VUS (Henneman et al., 2016; de Wert et al., 2021). Criteria for variant interpretation include the congruity with a defined clinical phenotype and the segregation of the variant in the family. In a context of asymptomatic population carrier screening, variant classification is particularly challenging due to the absence of a phenotype, with a much higher chance of false negative and false positive results. Therefore, ECS reporting strategies should focus on P/LP variants only to maximize analytical specificity (Vintschger et al., 2023). There should be no disclosure to couples of VUS or variants that are not clearly pathogenic in reports of carrier screening tests for reproductive decision

making. ESHG and ESHRE recommended to preferably store the findings regarding VUS in databanks, in order to allow their inclusion in research aimed at clarifying genotype–phenotype correlations (van El et al., 2013; de Wert et al., 2021). Those variants databases are expanding, particularly from affected individuals, and the current ability to interpret sequence variants is continuously evolving. This would advance VUS re-classification as likely pathogenic or likely benign and will increase the accuracy of variants interpretation for future use (Fridman et al., 2020).

Another cluster of issues related to the introduction of ECS is linked with the principle of respect for (reproductive) autonomy. According to the respondents from centres offering ECS that answered the question on counselling, most centres offer both pre- and post-test counselling related to ECS. Some respondents mentioned challenges for counselling as a consequence of the composition of the panel, e.g. because of broad panels or including milder disorders. One issue regards the means to make the respect of autonomy operational: the prerequisite of informed consent. How to avoid information overload and how to assure informed consent in complex genomic screening, particularly when pre-test counselling is not offered? Especially challenging are disorders where the result has personal health implications for carriers, for instance, female carriers of the Fragile-X premutation, are at risk for developing premature ovarian insufficiency (Gbur et al., 2021).

Clinical geneticists prioritize patient autonomy, reflecting the ethos of non-directiveness in clinical genetics. Conversely, reproductive physicians face moral tensions regarding respecting autonomy versus considering the welfare of potential children in MAR. When confronted with couples carrying a severe genetic disorder, ESHRE suggests that access to MAR may be ethically justified only if the couple agrees to preventative measures (de Wert et al., 2021). However, survey responses reveal varied centre policies, with nearly half requiring preventative measures for MAR access, yet this is not universally recognized as a moral dilemma.

The offer of ECS is also associated with issues linked with the principle of justice. According to respondents, ECS is not offered systematically to all MAR patients but is most commonly offered to MAR couples who request the test themselves or to couples who are consanguineous. Thus, those couples aware of screening and potentially more highly educated may more often obtain screening. One of the main reasons for not offering ECS was the high cost for couples or the unavailability of reimbursement, with respondents also noting cost as a challenge or moral dilemma. The relative high cost of comprehensive genetic testing and the lack of a systematic approach to offering ECS by the European MAR centres raises the more general issue of equity of access to ECS, which has also been acknowledged by couples themselves (van Dijke et al., 2021).

Given the scarcity of resources, the opportunity costs need justification, especially expenditure in publicly funded health care systems. Would it be ethically sound to also take account of any cost savings, assuming that many couples carrying a serious recessive disorder will opt to avoid the conception or birth of an affected child? Experiences exist where ECS was implemented with a propositional approach, by targeting only a core of severe and well-known conditions at a cost equivalent to that of a CF screening alone (Capalbo et al., 2019). Some cost-effectiveness analyses are available in the literature, where the cost of screening is beneficial/favourable as compared to the cost of treatment of affected babies (Musci and Caughey, 2005; Norman et al., 2012; Beauchamp et al., 2019; Busnelli et al., 2023).

Several challenges, as discussed above under the heading of proportionality, autonomy, and justice, have been previously reported on the implementation of ECS (Manolio et al., 2013; Holtkamp et al., 2017; Shen et al., 2022; Pasquier et al., 2023).

While the primary focus of the survey regards the offer of ECS to applicants of MAR, it reveals some interesting data regarding carrier screening in gamete donors as well. ESHRE warned that although it may be tempting to consider ECS of gamete donors as simply part of reproductive physicians' responsibility to minimize risk for children thus conceived, the case for ECS of donors is not obvious (Dondorp et al., 2014). As a minimum, donors should not be reduced to the gametes that they are willing to provide—any screening of donors requires their informed consent and adequate counselling on its implications. Of the respondents that answered the question of whether their centre offers ECS to gamete donors 62.4% (53/85) indicated this to be the case. Lack of counselling is a lost opportunity not only for minimizing ECS's risks of psychosocial harm in case of an unexpected positive result, but also for facilitating well-considered decisions of candidate donors. A standardized panel including specific sets of genes associated with comprehensive lists of disorders and allowing matching donors and recipients would be beneficial for people in need for fertility care (Payne et al., 2021).

Limitations

This survey had several limitations including the suboptimal completion rate, as some respondents did not answer all the questions. It was also difficult to distinguish between private and public practices; this distinction was not previewed upfront for all options. Furthermore, response and non-response bias are acknowledged as a further limitation. It is also plausible that some questions were not easily understood by the respondents. However, this survey clearly showed the heterogeneity in the current practice of ECS and highlighted the need to define the minimum requirements regarding clinical and analytical validity, and to refine the criteria to standardize the ECS implementation.

Conclusion

Our results show limited support and substantial heterogeneity in MAR centres offering ECS both for carrier couples and gamete donors. Heterogeneity of panels, issues with variants interpretation, counselling, lack of recommendations supporting ECS, and costs represent the main barriers for broad implementation and a working area for further development of scientific/practice guidelines. The few existing national recommendations and low awareness of existing international recommendations, calls for better dissemination strategies of the existing guidance. Moreover, given the many open questions, weighing the pros and cons on ECS requires more data to substantiate and guide further implementation. Therefore, earlier calls from ESHRE to embed ECS offers in (multidisciplinary) research, aimed at gathering relevant data, are still crucial (de Wert et al., 2021).

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

The majority of the data underlying this article is available in the article and in its online [supplementary material](#). Unpublished

data will be shared on reasonable request to the corresponding authors.

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Authors' roles

A.C., representing ESHRE, and F.F., representing ESHG, co-chaired the working group. All authors contributed equally to the conception and design of the survey, the analysis of the results, drafting the article, and revising it critically. All authors approved the final version of the paper.

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Conflict of interest

A.C. is full-time employee of Juno Genetics. L.H. declared receiving a research grant during the past 36 months from the Netherlands Organisation for Health Research and Development. She has also participated in a Health Council report of the Netherlands on preconception carrier screening and collaborated with the VSOP Dutch Genetic Alliance (patient umbrella organization on rare and genetic disorders). L.H. and C.v.E. are affiliated with Amsterdam University Medical Centre, a hospital that offers expanded carrier screening in a non-commercial setting. R.V. received honoraria for presentations from Merck Academy and is unpaid board member of the executive committee of the Spanish Fertility Society. The other authors had nothing to disclose.

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