ESHRE Good Practice Recommendations on Expanded Carrier Screening in Medically Assisted Reproduction

Running title

Good practice on ECS

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Abstract

Study question: What are the key recommendations for the clinical implementation and technical aspects of expanded carrier screening (ECS) in medically assisted reproduction (MAR)?

Summary answer: The present ESHRE Good Practice Recommendation document provides practical guidance on the clinical, technical, ethical, and organisational aspects of ECS implementation in MAR, with the aim of supporting consistent, equitable, and informed reproductive decision-making.

What is known already: ECS allows the identification of individuals or couples at risk of transmitting autosomal recessive or X-linked conditions and is increasingly used in reproductive care. However, significant variability exists in panel design, reporting, counselling, and clinical implementation, and existing international guidelines from professional societies do not fully address ECS implementation in MAR settings.

Study design, size, duration: These recommendations were developed by an ESHRE working group in accordance with the ESHRE methodology for Good Practice Recommendations.

Participants/materials, setting, methods: The working group included multidisciplinary experts in reproductive genetics, clinical embryology, ethics, and bioinformatics supported by methodological experts. Recommendations were developed based on a structured review of the literature combined with expert consensus. A stakeholder review was organized following completion of the draft, and the final version was approved by both the working group, and the ESHRE Executive Committee.

Main results and the role of chance: This Good Practice Recommendation document provides recommendations on eligibility and timing of ECS in MAR, gene panel selection and validation, result interpretation and reporting strategies, genetic counselling and informed consent, as well as ethical and technical considerations. Emphasis is placed on supporting informed reproductive choice, equitable access, and integration of ECS within existing reproductive care pathways.

Limitations, reasons for caution: The recommendations are based on expert consensus informed by available evidence, which remains heterogeneous and continues to evolve. Differences in healthcare systems, regulatory frameworks, and resource availability may require local adaptation.

Wider implications of the findings: These recommendations aim to support harmonisation of ECS practices in MAR, improve clinical consistency, and guide responsible implementation across diverse healthcare settings.

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Disclaimer

This Good Practice Recommendation (GPR) document represents the consensus views of the members of this working group based on the scientific evidence available at the time of the meeting. GPRs should be used for information and educational purposes. They should not be interpreted as setting a standard of care or be deemed inclusive of all proper methods of care or be exclusive of other methods of care reasonably directed to obtaining the same results. They do not replace the need for application of clinical judgement to each individual presentation, or variations based on locality and facility type.

Keywords

ESHRE, guideline, good practice, Expanded carrier screening; ECS; medically assisted reproduction; MAR; genetic counselling; reproductive genetics; gene panel design; variant interpretation; laboratory methods; analytical validity; gamete donation; informed consent; clinical implementation.

Introduction

Expanded Carrier Screening (ECS) for reproductive purposes, also known as Reproductive Genetic Carrier Screening, is a genetic testing strategy intended to identify individuals or couples who carry pathogenic/likely pathogenic variants (P/LP) in genes associated with autosomal recessive (AR) or X-linked recessive (XLR) conditions, with the primary aim of enabling informed reproductive decision-making. Ancestry-based carrier screening programs first emerged in the 1970s, driven by population-specific founder effects leading to increased risk of particular disorders in defined populations; a notable example is the Ashkenazi Jewish community, where a high carrier frequency for Tay-Sachs disease prompted widespread screening initiatives that led to a significant decline in disease incidence (King and Klugman, 2018), while similar ancestry-based initiatives were introduced in Europe — for instance in Cyprus, where β-thalassemia screening programs launched in the 1970s led to a substantial and sustained decline in births of children with β-thalassemia major (Bajaj and Gross, 2014, Cousens et al., 2010). However, such targeted population-screening strategies are inherently limited, as they usually inform only on risk for the most common genetic conditions within a population and fail to identify at risk couples (ARCs) for other potential disorders, including those that are rarer within the predefined population or geographic group.

Over the past decade, advances in genomic technologies — particularly high-throughput sequencing (HTS, also referred to as next-generation sequencing, NGS) — have enabled the development of multiplexed, cost-efficient panels capable of screening hundreds of genes simultaneously (Lazarin and Haque, 2016), shifting the field toward a universal, pan-ethnic, population-based model that identifies ARCs regardless of ancestry or family history. This pan-ethnic approach addresses increasing population diversity and the limitations of self-reported ancestry, thereby improving detection accuracy, promoting health equity, and expanding clinical applicability (ACOG, 2017a, Gregg et al., 2021, Vendrell et al., 2025). ECS is now

progressively adopted in medically assisted reproduction (MAR), including gamete donation, reflecting increasing recognition of its clinical utility in identifying ARCs and informing reproductive decision-making before conception, and underscoring its value as a proactive tool for preventing the transmission of severe monogenic disorders while supporting patient autonomy through informed choice.

Recent large-scale initiatives and pilot programs have firmly established the clinical utility and operational feasibility of ECS: the Australian Mackenzie's Mission project demonstrated that a coordinated, couple-based screening model for hundreds of severe genetic conditions can be successfully implemented at a national scale (Kirk et al., 2024), complementing earlier findings by Johansen Taber *et al*. (2019) which underscore the high degree of actionability inherent in ECS results for ARCs identified prior to conception (Johansen Taber et al., 2019). European implementation studies have further confirmed that diverse delivery models are both feasible and highly acceptable to the public, with the Groningen pilot study successfully utilising trained general practitioners to offer screening (Schuurmans et al., 2019), and the Amsterdam UMC study demonstrating that university hospital-based programs facilitate high levels of informed choice and patient satisfaction (van Dijke et al., 2021).

Despite these recognised benefits and the recommendations of multiple published scientific and professional societies regarding ECS usage (ACOG, 2017a, ACOG, 2017b, Health Council of the Netherlands, 2023, RANZCOG Genomics Advisory Working Group & Women's Health Committee, 2024, Aul et al., 2025, Capalbo et al., 2022, Edwards et al., 2015, Gregg et al., 2021, Guha et al., 2024, Henneman et al., 2016, Sagaser et al., 2023, Vendrell et al., 2025), significant heterogeneity persists in clinical practice globally. Regional variation remains pronounced: for example, the Japan Society of Human Genetics (JSHG) restricts carrier testing to individuals with a known family history of a specific genetic disorder, and the 2023 Human Genetics Society of Australasia (HGSA) position statement focuses exclusively on cascade testing in relatives of affected individuals without addressing population-based or reproductive carrier screening (Vears et al., 2023), highlighting that clinical endorsement of universal, population-based ECS is not yet uniform across regions. The main gaps across existing guidelines are highlighted in Table 1 and concern the variability in defining the target population and timing of screening; lack of consensus on gene panel development, validation, and variant reporting — particularly regarding variants of uncertain significance (VUS) and residual risk; inconsistent requirements for informed consent and counselling; variable approaches to partner testing, recontact, and follow-up responsibilities; and uneven standards for quality, accreditation, and equity. At a technical level, a recent analysis of 22 ECS panels comprising 2,205 unique genes revealed that the number of genes included in individual panels ranged from 44 to 2,054, with only 15 genes (0.7%) shared across all panels, and considerable variation in cost, with no significant correlation between panel price and gene count (Wang et al., 2023); furthermore, the limited representation of many populations in genomic databases continues to affect the accuracy and equity of testing outcomes.

These clinical and technical limitations are especially consequential in MAR, where treatment decisions are time-sensitive and donor programs require clear, standardised pathways. A recent ESHG–ESHRE-led survey on the practice of ECS in MAR confirmed considerable variability amongst centres, with the primary reason for non-implementation being the absence of professional recommendations supporting its use (Capalbo et al., 2024), emphasising the urgent need for evidence-based guidelines to ensure consistent, equitable, and ethically sound ECS delivery.

Box 1. Background

Mendelian disorders primarily result from mutations in a single gene (monogenic) and typically exhibit either recessive or dominant inheritance patterns. Autosomal recessive disorders include a wide variety of conditions, collectively representing a significant portion of single-gene disease burden, with an estimated prevalence of approximately 2.7 per 1,000 live births (Xiao and Lauschke, 2021), making them more common than individual chromosomal conditions such as Down syndrome (approximately 1 per 1,000 live births) (WHO, 2021). Since carriers of most autosomal and X-linked recessive conditions are typically asymptomatic, most couples remain unaware of their potential risk of having an affected offspring. A recent study estimated that approximately 4% of couples are at risk of having a child with a recessive genetic disorder (Lee et al., 2025a), with 2% being of high severity and life-threatening. Moreover, the vast majority of these children diagnosed with a recessive genetic condition do not have a prior family history of the disease (Lazarin et al., 2014). This underscores the limitations of relying solely on family history to assess genetic risk in couples planning a pregnancy.

No international guideline currently addresses the complete framework of ECS specifically within the MAR setting and gamete donation. The present document therefore aims to establish Good Practice Recommendations (GPRs) covering: (1) clinical implementation and management pathways; (2) genetic counselling requirements including pre- and post-test protocols and informed consent; (3) ethical and legal frameworks addressing equity of access, data privacy, and reporting thresholds; (4) technical considerations including panel design, analytic and clinical validity, and variant interpretation; and (5) future research priorities — to promote standardised, ethical, and effective ECS implementation in MAR practice that can meaningfully support informed reproductive decision-making.

At a broader level, system-level barriers towards implementation - including unequal access, limited counselling/laboratory capacity, and differences in funding, regulation, and professional training - lie largely outside what professional guidance can address.

165 *Table 1. Overview of professional society recommendations on carrier screening and ECS.*

Issuing body (reference)	Population	Timing	Conditions	Reporting	Consent	Counselling	Partner Testing	Quality & Notes
EUROPE								
ESHG (Henneman et al., 2016)	Individuals or couples	Preconception preferred	Severe childhood-onset disorders; proven clinical validity; no panel defined.	Only clinically significant variants reported; Reports must address residual risk	Generic model proposed to manage "information overload"-it requires evaluation; pre-test information mandatory with sufficient time to decide. Consent must ensure informed and voluntary participation.	Generic pre-test information for all (through electronic communication); individual pre-test counselling available on request; post-test counselling offered/strongly recommended for carrier couples. Counselling to include discussion on residual risk, test limitations and implications for relatives	All approaches discussed (simultaneous/sequential, individual/couple-based), no fixed recommendation. Notes that couple-based disclosure reduces anxiety	Testing in accredited laboratories; framework emphasizes reproductive autonomy, informed choice, governance, equity, **evidence base**; participation in carrier screening is voluntary; calls for professional training, government oversight, and equitable access. ECS success should be measured by the quality of informed choice/ reproductive autonomy rather than a reduction in the birth prevalence of affected children
SIGU (Capalbo et al., 2022)	Reproductive-age couples (natural or MAR); consanguinity; gamete donation	Preconception preferred; ≤12 weeks acceptable	Panel: Severe/early-onset with well-defined phenotype; unfavourable effect on the quality/duration of life, causative of "physical and/or cognitive impairment" and require "medical and/or surgical intervention, diagnostic procedure or PGT available; no fixed list.	Report P/LP only. VUS should not be reported; include residual risk in report	Consent mandatory (template provided). State that screening is voluntary and that residual risk remains.	Pre- and post-test essential; interpretation guidance required.	Simultaneous preferred (especially in pregnancy), sequential acceptable.	Preclinical validation and quality criteria required; equitable access, inclusivity and cost-effectiveness emphasized. NGS recommended; ancillary testing (e.g. MLPA) mandatory for complex genes (SMA, Fragile X)
Health Council of the Netherlands (2023)	All prospective parents in the Netherlands (population-wide/ universal offer)	Preconception	Strictly targets severe hereditary disorders; explicitly must not target increasingly milder disorders to prevent 'designer babies'.	Findings with certain clinical relevance	Voluntary participation; informed consent central. Prospective parents completely free not to participate.	Pre-test education and counselling essential.	Couple-based risk assessment preferred (pilot model)	Advisory Report: Primary objective is to enhance reproductive autonomy. Advises government to launch a large-scale scientific pilot for universal ECS, to evaluate effectiveness, feasibility, equitable access, and psychological impact of a population-wide offer.
AEGH, AEDP, ASEBIR, SEAGAN, SEF and SEGCD (Spanish societies) (Vendrell et al., 2025)	General population; reproductive age	Preconception preferred	Severe, early-onset conditions with well-defined phenotypes; distinct from "mild" or adult-onset disorders. Recommends a basic panel (CFTR, SMN1, GJB2, hemoglobinopathies, and FMR1 in women) as well as extended GCS panels.	Pathogenic/Likely Pathogenic (P/LP) only. Incidental findings can occur and must be discussed.	Informed consent essential; Must explicitly cover the voluntary nature of screening, residual risks, and potential for incidental findings.	Mandatory, exhaustive pre-test and post-test genetic counselling required.	Couple-based results reporting is preferable	Recommends shifting from ethnicity-based to universal pan-ethnic preconception screening within the public health system. Emphasizes equity, reproductive autonomy, and the necessity to guarantee analytical/clinical validity and utility.

NORTH AMERICA								
ACOG (2017a, 2017b) (reaffirmed 2025)	All pregnant/planning pregnancy; For Fragile X: women with POI or elevated FSH <40 years, relevant family history or on request	Preconception preferred	SMA, CF, Hb disorders for all; TSD (Ashkenazi/French-Canadian/Cajun/family history) +13 Ashkenazi conditions; ECS is optional; enzyme testing recommended for high-risk groups for Tay-Sachs disease. ECS panel ≥1/100 (ACOG 690: population not specified). Adult-onset conditions should be excluded	Identifies variants associated with a diagnosis (P/LP). Does not require or recommend numerical residual-risk reporting but residual risk must be discussed)	Informed consent is necessary; pre-test consent must describe the voluntary nature of testing, condition types and screening limitations.	Pre-test counselling for all; post-test for carrier couples; residual risk should be explained; If a carrier is identified, the reproductive partner should be offered screening to provide accurate genetic counselling for the couple regarding the risk of having an affected child. Tailored counselling for Fragile X intermediate, premutation, and full-mutation results.	Sequential preferred; concurrent if time-limited	Analytical validity required; disclosure to relatives encouraged; cost and access considerations noted. ECS is optional; prenatal screening distinguished from newborn screening.
ACMG (Gregg et al., 2021, Guha et al., 2024)	Population-neutral; all pregnant/ planning	Preconception or prenatal	Tier-based approach. Tier 1: SMA, CF; Tier: 2 ≥1/100 severe/moderate conditions- defined in any U.S. subpopulation**,** no fixed list; Tier 3 (recommended standard): **≥1/200** (list of 97 AR + 16 XLR conditions,); Tier 4: <1/200 recommended only for consanguinity or family history Equity and severity emphasized; Offering only Tier 1–2 is discouraged	P/LP only, VUS generally not reported. May be disclosed selectively. Residual risk must be discussed; numerical estimates often avoided due to imprecision	Participation is voluntary. Separate consent specifically required for reporting VUS/secondary findings.	Pre- and post- test required. For at-risk couples, counselling should cover all reproductive options	Sequential or simultaneous during preconception; simultaneous (concurrent) highly recommended during an ongoing pregnancy	Analytical validity and ongoing curation emphasized; equity addressed 2024 Technical Standard mandates ancillary technologies (e.g., MLPA) or validated custom NGS callers for technically challenging genes (e.g., SMN1, FMR1, GBA, CYP21A2). Reproductive decision making is the established metric for ECS' clinical utility.
CCMG (Aul et al., 2025)	All individuals considering a pregnancy (preconception), all pregnant individuals (regardless of gestational age), and their reproductive partners	Preconception preferred; or as early in the pregnancy as possible	Pan-ethnic screening for CF, SMA, Fragile X, haemoglobinopathies, and founder mutations for Tay-Sachs, Canavan, and familial dysautonomia. Maintain regional ethnicity-based screening (e.g., Indigenous, French Canadian).	P/LP only for the targeted conditions. Do not report VUS	Offered as an opt-in test; an initial discussion about the value and risks of screening must be offered to all individuals to support informed decision-making.	Pre-test: Must ask about family history and refer high-risk individuals to a Genetics clinic for counselling. Post-test: Carrier couples must be referred for formal genetic counselling. Focus on informed decision-making.	For limited panel: sequential preconceptionally; concurrent in ongoing pregnancy to expedite results.	Retires the 2016 ethnicity-based guideline. Supports equity via a targeted pan-ethnic panel but cites resource/system constraints for full ECS. Explicitly requires the development of coordinated provincial/territorial programs for oversight, education, and implementation. Publicly funded ECS is not recommended. Primary goal: to provide information about reproductive risk for informed decision-making
NSGC (Sagaser et al., 2023)	Pregnant/planning or biologically contributing to pregnancy	Preconception preferred	AR and XLR conditions relevant to reproductive planning or neonatal care no specific clinical criteria or tiers.	Reporting guided by laboratory policy and informed consent;	Essential; Utilizes "KINDS" elements (Knowledge, Inheritance,	Pre- and post-test counselling recommended; patient-centred and non-directive approach.	Simultaneous preferred (especially in pregnancy)	Focuses on patient-centred communication and implementation; promotes equitable access within a

				VUS not routinely reported; incidental findings may occur	Normalization, Discrimination, Surprise results). Must include incidental findings, VUS and reinterpretation.	Electronic communication suggested as a time management tool to aid the offering and delivery of ECS		reproductive-justice framework that prioritises informed choice and inclusion. Supports eliminating race-based medical practice.
AUSTRALASIA								
RANZCOG (2024)	All couples intending to have children, or who are pregnant women/ couples	Preconception or 1st trimester of pregnancy; Preconception preferred	Basic screening for thalassaemia (via full blood examination) recommended for all. CF, SMA, Fragile X (3-condition panel) recommended for all; ECS acceptable with appropriate counselling pathways; with additional screening for Ashkenazi Jewish (Eastern European) descent. Panels should focus on serious, early-onset conditions that cause major diminution of quality of life and/or reduction in lifespan	Class 4–5 variants must be reported, VUS should not be reported.	Written informed consent required. Must include residual risk, chance of being affected, out-of-pocket costs and the results become invalid if the individuals change reproductive partners for future pregnancies.	Pre- and post-test essential. Must begin with taking a family history to refer high-probability individuals directly to genetic services	Sequential (woman first) or couple-based	Laboratories must be NATA/IANZ accredited; update emphasizes equity and access. Australian Medicare rebate applies only within a sequential screening approach (woman tested first).

ACMG: American College of Medical Genetics and Genomics; ACOG: American College of Obstetricians and Gynaecologists; AEDP: Asociacion Espanola de Diagnostica Prenatal (Spanish association of Prenatal Diagnosis); AEGH: Asociación Española de Genética Humana (Spanish Association of Human Genetics); AR: autosomal recessive; ASEBIR: Association for the Study of Reproductive Biology; CCMG: Canadian College of Medical Geneticists; CF: cystic fibrosis; ECS: expanded carrier screening; ESHG: European Society of Human Genetics; FMR1: Fragile X messenger ribonucleoprotein 1; FSH: follicle-stimulating hormone; FXS: Fragile X syndrome; GCS: Genetic carrier screening; IANZ: International Accreditation New Zealand; MAR: medically assisted reproduction; MLPA: Multiplex ligation-dependent probe amplification; NATA: National Association of Testing Authorities); NGS: Next-generation sequencing; NSGC: National Society of Genetic Counsellors; PGT: preimplantation genetic testing; P/LP: pathogenic/ likely pathogenic; POI: primary ovarian insufficiency, RANZCOG: Royal Australian and New Zealand College of Obstetricians and Gynaecologists; SEAGEN: Sociedad Espanola de Asesoramiento Genetico (Spanish Society of Genetic Counselling); SEF: Sociedad Española de Fertilidad (Spanish Fertility Society); SEGCD: Sociedad Espanola de Genetica Clinica y Dismorfologia (Spanish Society of clinical genetics and Dysmorphology); SIGU: Italian Society of Human Genetics; SMA: spinal muscular atrophy; SMN1: Survival motor neuron 1; TSD: Tay–Sachs disease; VUS: variant of uncertain significance; XLR: X-linked Recessive.

Where multiple societies contributed to a consensus statement, selected representative societies are listed followed by 'et al.' for brevity.

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Methodology

The current document was developed according to the manual for development of ESHRE Good Practice Recommendations (Vermeulen et al., 2019).

A working group (WG) was composed of members of the ESHRE Special Interest Groups (SIG) Reproductive Genetics, Ethics and Law, and invited experts in the field, ensuring representation of clinical and laboratory expertise, and geographical balance, supported by methodological experts (NLC and SM). In the first meetings, the WG reached agreement on a list of topics to be addressed in this recommendations paper. Data on expanded carrier screening published were collected from the literature in PubMed/Medline and relevant papers included in the text. Studies not published in English were excluded. References retrieved from the literature search were complemented with further key references identified by the WG members. The recommendations for clinical practice were formulated based on expert opinion of the WG, taking into consideration the available evidence.

The final draft was made available on the ESHRE website between 14 May and 11 June 2026 for stakeholder review.

An overview table with all abbreviation used in this Good Practice Recommendations paper can be found in Supplementary table S1. An overview of all recommendations formulated by the ESHRE working group on ECS can be found in Supplementary table S2. Recommendations for future research can be found in Supplementary table S3.

Results

Clinical implementation of ECS in MAR

Indications, timing and clinical implementation of ECS in MAR

The timing and setting in which ECS is offered warrant careful deliberation, as these factors significantly influence cost-effectiveness, uptake rates, and the range of reproductive options available to prospective parents. MAR patients already undergo an intensive medicalised reproductive process, which may influence the perceived added value of additional testing. It is also important to emphasise that, while ECS does not influence the clinical success rates of MAR procedures, it plays a key role in supporting informed reproductive decision-making for couples and may inform adjustments in their clinical or reproductive management. Consequently, ECS is increasingly offered as an option for all couples undergoing MAR.

ECS can be offered at several life stages such as during the preconception period, or prenatally (Rowe and Wright, 2020). One of the main challenges of offering ECS at the preconception stage is the difficulty of reaching the general population, due to the current lack of a dedicated preconception care infrastructure. In contrast, patients undergoing MAR represent a readily accessible and particularly appropriate population for ECS. In the context of MAR, the preconception period is generally considered the most suitable time for offering ECS, as it

maximizes the reproductive choices available to couples, thereby supporting truly informed decision-making (Henneman et al., 2016).

There are two different approaches with regards to offering ECS to couples: simultaneous (parallel) screening and sequential screening. Each strategy presents distinct advantages and limitations in terms of cost, emotional impact, logistics, and the impact on reproductive decision-making.

In the simultaneous screening approach, both partners are tested at the same time, providing a comprehensive risk assessment. By identifying the carrier status of both individuals concurrently, clinicians can immediately evaluate the couple's risk. This facilitates timely reproductive decision-making and avoidance of delays in fertility treatment—an important factor for patients undergoing MAR, as one of the key reasons couples decline ECS is concern over treatment delays (Frank et al., 2025).

Nonetheless, simultaneous screening is not without challenges. The primary drawback is increased upfront cost in addition to receiving potentially complex genetic information for both partners at once leading to emotional distress or confusion (Frank et al., 2025).

Sequential screening, in contrast, involves testing one partner first—and only proceeding to test the second partner if the first is found to be a carrier of a condition included in the screening panel. However, waiting for the results of the first test before initiating testing of the second partner can slow down reproductive planning. Moreover, if the second partner is never tested—whether due to oversight or other challenges, the couple's reproductive risk may remain incompletely assessed, undermining the goals of ECS.

The evidence increasingly supports simultaneous screening as the preferred approach (Kirk et al., 2024). It maximises the clinical utility of ECS by allowing for immediate risk assessment and early intervention and helps avoid additional delays.

In addition to offering ECS to couples, the test is increasingly offered to gamete donors in the context of MAR. Many gamete banks, particularly in Europe and the United States, routinely perform ECS on all prospective donors. Nevertheless, the introduction of ECS in this setting must be accompanied by safeguards to mitigate potential drawbacks. These might include the provision of thorough genetic counselling and the restriction of ECS panels to well-characterised, severe, recessive conditions with appreciable carrier frequencies (Dondorp et al., 2014). The long-term implications for the donor-conceived child, as well as for the donor, should also be considered.

Recommendations

All individuals undergoing MAR, including gamete donors, are eligible for ECS.
The preconception period is the preferred timing for ECS in MAR to maximise clinical and reproductive benefit.
It is recommended to do simultaneous testing of both partners.

Choosing the appropriate gene panel

When offering ECS in MAR settings, it is important to select a test that is evidence-based, aligned with professional society guidelines, and clinically meaningful. ECS should help identify couples or gamete donors at risk of transmitting serious inherited conditions, while avoiding unnecessary testing or ambiguous results (Henneman et al., 2016). The size and scope of the ECS panel should be appropriate for the target population and clinical context. ECS panel design should also consider ethnic and population-specific prevalence of genetic disorders, ensuring that conditions with meaningful carrier frequencies in the target population are included. This approach maximises clinical utility and detection yield while avoiding unnecessary expansion to ultra-rare or poorly characterised disorders that lack clear or established clinical significance, which may otherwise increase uncertainty in interpretation and counselling burden.

However, broader panels that include rarer conditions may be appropriate in selected contexts. For example, in consanguineous couples, where the likelihood of shared rare recessive variants is increased, the inclusion of less common but clinically relevant disorders can improve diagnostic sensitivity and reproductive risk assessment. In such scenarios, the potential benefits of expanded screening may outweigh the limitations associated with lower-prevalence conditions, particularly when supported by robust gene–disease associations and clear phenotypic relevance.

ECS should focus on both AR and XLR, serious, congenital and childhood-onset diseases (Henneman et al., 2016). While it is difficult to agree on an operational definition, general criteria for seriousness typically include factors like reduced life expectancy, intellectual or mobility impairments, adverse impacts on functioning, frequent hospitalisation, and reduced quality of life. In this respect, it is essential to consider the expertise of genetic and paediatric professionals, as well as the lived experience of affected families, when deciding on and updating the screening panel (Kleiderman et al., 2025).

It is important to recognise two additional points in gene panel selection: (i) conditions included in newborn screening programs may also be appropriate for inclusion in ECS panels, as the two serve distinct but complementary purposes; and (ii) ECS panel design should not be restricted to conditions eligible for preimplantation genetic testing for monogenic disease (PGT-M), as broader panels may support informed reproductive choices through alternative options. This is particularly relevant in light of the considerable variation in policies and regulations governing NBS and PGT-M across countries.

The testing platform must be analytically validated to ensure high accuracy in variant detection, including single-nucleotide variants, small insertions/deletions, and relevant copy number changes. The testing laboratory should hold appropriate accreditation (e.g., ISO, CLIA, CAP) and maintain robust quality assurance processes. Moreover, the lab should have a clear,

documented framework for how panels are designed, curated, and updated, with defined criteria for gene and variant inclusion based on clinical evidence (more detailed information is described in the technical section). Reports should be clear, focus on clinically actionable findings, and include only pathogenic and likely pathogenic variants, with appropriate guidance for follow-up where relevant. This ensures that both clinicians and patients can accurately understand the implications of the results and make informed decisions (Richards et al., 2015).

Recommendations

ECS panels developed through transparent, evidence-based processes aligned with professional society guidelines should be selected.
Serious, early-onset, and clinically well-defined AR and XLR disorders with clear genotype-phenotype correlations should be prioritised.
Panel inclusion should not be restricted to conditions currently eligible for PGT-M or listed in national pre-approved gene lists, provided they meet established clinical validity and severity criteria.
Conditions included in newborn screening programs should be considered for inclusion when they provide clear reproductive benefit.
Gene panels should undergo periodic re-evaluation to incorporate newly validated gene–disease associations, improved variant annotation, and refined severity frameworks.
Clear documentation should be available on the methodologies used to define gene-panel content, and reporting policies.
ECS test should be analytically validated, performed in an accredited laboratory, and accompanied by clear and clinically interpretable reports.
Reporting should be limited to pathogenic and likely pathogenic variants.

Interpretation and reporting of results

Strategies for reporting of ECS results

Autologous cycles

In the context of autologous MAR, and assuming testing was performed simultaneously, ECS results may be reported individually to each member of the couple (individual reporting) or a combined report as a couple (couple-based reporting).

In individual reporting, each member of the couple receives their personal report. This approach offers the advantage for each partner to know their carrier status, enhancing their present and future reproductive autonomy and allowing family cascade testing in case of a positive result. However, individual approaches are costly, especially due to the need for more extensive post-test counselling. It may also heighten anxiety through the disclosure of findings with limited reproductive relevance, uncertainty, and delays for couples undergoing an already stressful procedure, as it increases the likelihood of requiring addressing the conditions each

partner may carry. Moreover, individual reporting requires an expert interpretation of both reports to ensure any reproductive risk for the couple has been identified.

In couple-based reporting, in contrast, a single report is provided, which only includes an evaluation of the couple's reproductive risk(s) (high reproductive risk vs. low reproductive risk) without disclosing the pathogenic variants carried by each individual. Couple-based reporting is therefore more meaningful, as it is more closely aligned with the primary aim of ECS: to identify only those couples at significant risk of having an affected child—namely, carrier couples (for AR disorders) and female heterozygous carriers (for XLR disorders) (de Wert et al., 2021). However, this couple-based approach also carries its own limitations. First, individuals have the legal right to request their individual report, which may result in an unnecessary increase in costs, as separate interpretation and reporting are required in addition to the couple-based assessment, thereby duplicating clinical efforts (Plantinga et al., 2019, Van Steijvoort et al., 2020). Moreover, the identification of an incidental finding (IF, see section "Incidental and secondary findings") may require disclosure of individual results if clinically significant. In addition to the previous limitations, couples later requiring gamete donation or individuals returning in the future with new partners may also require new reports, or in some cases, being retested.

Irrespective of the reporting model used, individuals should retain the right to access their personal genetic information. Access to these findings within a structured framework supports the preventive nature of screening and may inform future healthcare decisions. Where possible, individual reporting should be favoured as it enables patient autonomy and enables family cascading, which becomes fundamental for frequent disorders. However, both reporting strategies are acceptable, if clearly detailed during informed consent and if patients are given the option to opt-in and opt-out of individual reports. The prioritisation of one reporting strategy over the other needs to be assessed based on the availability of resources (reproductive options, genetic counselling, size of the panel, etc.) and local regulations.

Donation cycles

In gamete donation, for similar reasons outlined above, two strategies exist: i) providing the recipient with both their individual report and a genetic matching report, or ii) providing only a genetic matching report. In this context, some clinics adopt the latter approach, as disclosure of the recipient's individual results is not considered necessary for clinical decision-making. Operationally, this can be implemented by issuing a genetic matching report to the recipient that classifies reproductive risk, based on the recipient's ECS results, as low when an appropriate donor (e.g. not a carrier of genetic variants in the same genes identified in the recipient) has been assigned.

It should be noted that the increasing number of ECS panels that are available, as well as the marked heterogeneity amongst them (gene inclusion criteria, number of genes, variant reporting policies, etc), may pose an obstacle in combining individuals and gamete donors that

have been tested with different ECS panels. An alternative strategy is a stepwise or reflex testing approach (increasingly referred to as “match testing"), in which ECS is first performed in one member of the pair (recipient or donor), and the counterpart is subsequently tested only for the genes or variants identified in the index individual, enabling assessment of shared carrier status while avoiding redundant full-panel testing. However, when considering gamete donors, it would be appropriate, respecting their autonomy, to offer them the option to receive their individual results, following adequate genetic counselling about the scope and implications of testing, possible results and potential implications. Moreover, if additional genes may be tested for matching purposes, this should be clearly explained on the consent form, and donors should be given the opportunity to opt-out from this practice and to indicate whether they wish to be recontacted if any relevant additional findings are identified. ECS for gamete donors should, equally to recipients, be always accompanied by adequate genetic counselling.

Incidental and secondary findings

In the context of high-throughput sequencing technologies, incidental findings (IFs) and secondary findings (SFs) refer to results that are unrelated to the primary indication for the test. The main difference between these two is that IFs are discovered unexpectedly within the scope of the test (for example, an individual may be identified as a carrier of a pathogenic variant in ATM, which is associated with ataxia-telangiectasia when biallelic variants are present, and with an increased risk of hereditary cancer predisposition, particularly breast cancer, in heterozygous carriers.), while SFs are actively and deliberately looked for during the analysis as they are considered medically actionable (Lee et al., 2025b, Ormond et al., 2019) even though they are outside of the scope of the test (for example, actively analysing clinically relevant variants in autosomal dominant genes associated with hypertrophic cardiomyopathy, as they are clinically actionable). The American College of Medical Genetics and Genomics (ACMG) has elaborated a list of conditions they consider medically actionable and hence potentially reportable. In addition, most secondary findings are autosomal dominant, not recessive or X-linked (Lee et al., 2025b).

Considering that ECS is commonly performed on HTS panels or even whole exome sequencing (WES) panels, both SFs and IFs may occur. IFs in ECS can happen in the following scenarios:

1) Variants in apparent homozygosis or compound heterozygosis (leading to an unexpected diagnosis). This can be explained by variants in genes with marked incomplete penetrance, variable expressivity or late-onset of symptoms.
2) Genes with bimodal inheritance (some variants may also act as autosomal dominant).
3) XLR genes in which female heterozygotes may develop some symptoms.
4) Microdeletions or microduplications of several genes that may suggest a larger copy-number variation.

If the methodology of the ECS may lead to some IFs, this should clearly be specified on the informed consent form. Ideally, patients should be given the opportunity to opt out of IFs. When an IF is identified and reported, post-test genetic counselling should always be offered to explain the potential implications and refer to other specialists if necessary.

The inclusion of SFs in ECS is outside the scope of this GPR document (see section 'Future perspectives').

Interpretation of ECS results

As the objective of ECS is identifying reproductive risks to enable reproductive decision-making, interpretation of its results will depend on the context it is being applied.

In autologous cycles, the result from both couple members needs to be taken into account. Two situations should be considered as high risk: firstly, if both couple members are identified as carriers of clinically relevant variants in the same AR gene (or two different genes that are known to be inherited following a digenic pattern) and secondly if the female partner is identified as a carrier of an XLR disorder. Any other result (both negative, one positive and the other negative, or both positive but for different genes) will be considered as low-risk results. In gamete donation cycles, performing a "genetic matching" between patient and donor is a possibility. This implies assigning a donor that does not carry the P/LP variants in the genes for which a patient is identified as a carrier. It should also be noted that egg donors identified as carriers of P/LP variants in X-linked genes should be considered ineligible for donation.

ECS has several limitations (see section "Pre-test genetic counselling"). For this reason, a negative result is considered a "low-risk result", not a "no-risk result". The chance of having affected offspring after ECS (even for a disorder included in the test) is referred to as residual risk. Residual risks for specific genes/disorders are complex to quantify, and hence reporting individual residual risk is non-informative. Patients should be informed about ECS and residual risks during pre-test and post-test counselling. Any result combination that may lead to an increased residual risk should be communicated to the patients through adequate genetic counselling.

Recommendations

Two ECS reporting models can be considered:

1. Individual reporting: each individual receives their own ECS report, with results interpreted in the context of the specific couple.
2. Combined reporting: a combined report assessing the reproductive risk is provided (couple report in autologous cycles or genetic matching report in gamete donation cycles).

The choice of reporting strategy should be guided by available resources and local regulations during genetic counselling.

Individuals should retain the right to access their personal genetic information, regardless of the reporting model used.
All tested individuals, including donors, should have the opportunity to opt in or opt out of receiving individual-level results.
ECS may reveal incidental findings; this must be disclosed in the consent and individuals should have the option to opt out of receiving such findings.
Interpretation of ECS results should be seen in a binary high vs low risk fashion.
When panels differ between partners/donor–recipient, an alternative is performing reflex testing ("match testing"), in which ECS is first performed in one partner, and the counterpart is subsequently tested only for the genes or variants identified.

Genetic counselling and informed consent

The American National Society of Genetic Counsellors defines the concept of "genetic counselling" as "*the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates the following: i) Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence; ii) education about inheritance, testing, management, prevention, resources and research; and iii) counselling to promote informed choices and adaptation to the risk or condition*" (Resta et al., 2006).

In other words, genetic counselling can be defined as the communication process to support and guide individuals and/or families in navigating autonomous decision-making when facing genetic testing and/or a genetic diagnosis (Austin et al., 2014, Patch and Middleton, 2018).

Genetic counselling should be emphasised as a key requirement for any patient or couple considering performing ECS, considering its nature (screening test, being a risk-identification tool), implications (both reproductive and familial) and limitations. Genetic counselling should ideally be offered both before and after performing ECS. These two sessions are usually referred to as pre-test and post-test genetic counselling (Fonda Allen et al., 2016, Riley et al., 2012).

Pre-test genetic counselling

Pre-test counselling should cover several aspects in order to support the patients' decision - making and to guarantee their autonomy regarding genetic testing. First, it should be made clear to patients that ECS is optional, and patients are free to decline testing. In the case of donors undergoing ECS, it should be made clear that genetic testing is part of the pre-requirements to become a donor. Basic education on genetic concepts (such as AR and XLR inheritance patterns) should be provided. The scope and limitations (Table 2) of ECS should be discussed in depth, making sure any misconceptions or false expectations are properly disproven. Considering the inherited nature of the conditions included in ECS, patients should be aware that their findings may be significant for their direct relatives, especially for those conditions with higher prevalence in the general population.

Table 2. Key limitations of expanded carrier screening and their implications for clinical interpretation (ACOG, 2017a, Belnap et al., 2025, Gregg et al., 2021, Veneruso et al., 2022):

Limitation	Impact on ECS	Reference(s)
Scope of conditions assessed	Not all genetic and hereditary disorders will be tested (only selected known AR and XLR conditions). Therefore, conditions that do not follow these inheritance patterns will not be included (e.g., autosomal dominant, mitochondrial, polygenic, multifactorial, amongst others).	
Panel composition and selection criteria	Currently, thousands of AR and XLR conditions are known. However, most ECS panels are designed to only include a selection of disorders often based on clinical considerations such as age of onset, severity, prevalence and penetrance.	(Balzotti et al., 2020, Goldberg et al., 2023, Henneman et al., 2016).
Variant interpretation and reporting	Most laboratories will only report variants with well-established pathogenicity. Variant classification evolves as scientific knowledge develops, therefore the interpretation of a specific variant, and hence the result of a specific ECS, may change over time.	(Richards et al., 2015)
De novo mutations	Spontaneous (de novo) mutations cannot be detected and therefore are out of the scope of ECS.	
Technical limitations	Some technical limitations exist even for those genes and variants that are included in the assay (such as regions of high genomic homology, variants with low-coverage (no calls) or CNVs or complex rearrangements).	
Biological limitations	Some biological phenomena may limit the genetic analysis, like mosaicism or chimerism.	

Patients should understand that ECS is a screening test, designed to identify reproductive risk, allowing them to make reproductive decisions upon it. While ECS is deemed useful in identifying and mitigating such risks, by facilitating risk reduction for the tested disorders, it does not completely eliminate the risk of having children with a genetic disorder (Haque et al., 2016, Nussbaum et al., 2021).

Additionally, patients should also be made aware that the carrier status for most AR and XLR conditions does not imply any health burden to the individual. However, some exceptions may exist, as previously described in the section 'Incidental findings'. If IFs may occur in a specific ECS panel, this should largely be addressed in the pre-test genetic counselling session (Vendrell et al., 2025). Another aim of pre-test counselling should be anticipating possible results and potential actionability of findings (for example, the possibility of PGT-M if a risk is identified) (Gregg et al., 2021). When pre-test counselling is adequately performed, it ensures the autonomy of the patients on whether to perform the genetic test and helps in mitigating the psychological impact of all possible results (Culver et al., 2024).

In sequential testing strategies, informed consent should ideally be obtained from both members of the couple at the outset, including agreement to reflex testing of the second partner if pathogenic or likely pathogenic variants are identified in the first individual. If the

second partner subsequently declines testing, reproductive risk assessment may remain incomplete, and counselling should focus on residual risk and available reproductive options.

The decision to proceed with carrier screening should be guided by a shared decision-making process that considers each patient's individual characteristics, along with their personal values and preferences. For patients wishing to proceed with ECS, informed consent should be obtained in a document that reflects all the previous points.

Recommendations

Genetic counselling is essential for all individuals/couples considering ECS due to the test's screening nature, implications, and limitations.
Pre-test genetic counselling should be provided to support autonomous, informed reproductive decision-making.
Pre-test genetic counselling should provide clear education on the optional nature, scope, limitations, residual risk, possible incidental findings, and potential reproductive implications of ECS to support fully informed, autonomous decision-making before testing.
Informed consent should be obtained prior to ECS and should explicitly document that individuals/couples have been informed about the scope, limitations and implications of testing.

Post-test genetic counselling

The content of post-test counselling should be more specific and tailored to the patient's results and needs. Based on these results, three possible scenarios may arise: i) low-risk with negative result (no genetic variant was identified); ii) low-risk with a positive result in different genes between members of the couple or between patient and gamete donor; and iii) high-risk result (both members of a couple present with genetic variants in the same gene, or female patient is a carrier of an XLR condition). In the case of couple-reporting, only 2 options remain (low-risk and high-risk).

For patients with a low risk with negative result, the limitations of the test and residual risk should be covered to reduce the potentiality of false reassurance. Ideally, despite the negative result, the patients should be offered appropriate post-test genetic counselling to revisit the test's scope, limitations and residual risks, as well as to offer the possibility to express any doubts or concerns.

In those patients with a low-risk with a positive result, the discussion should be more detailed compared to those with a low-risk with negative result. Information on the identified conditions should be provided, adapting to the individual's information needs. Education on the pattern of inheritance should be offered, outlining the lack of health implications for the carrier (unless it is considered an IF, which will be described below). As most genetic variants identified during ECS may be inherited, sharing the results to close relatives to enable genetic counselling and testing should be advised. If patients express uncertainty or difficulties in

communication this information to family members, exploring some communication plans with them may prove beneficial. Family communication may be especially relevant when ECS results imply no reproductive risk, as patients may experience a false relief and decreased risk perception (Birnie et al., 2021, Cannon et al., 2023, McCormick et al., 2022, Strasser et al., 2025). For those results involving an IF, counselling should proceed with caution, especially if the result may carry a direct present or future health implication for the patient. When needed, referral to specialist care and/or psychological support should be recommended when disclosing IFs.

The same information as above should be provided to patients with a high-risk result when seen for post-test counselling, albeit significantly more nuance is required. Additionally, the potential reproductive risks should be extensively described, alongside a discussion of available reproductive options. The psychological impact when receiving high reproductive risks may be significant, and patients/couples may require some time to adapt to the new situation (Birnie et al., 2021). Patients in this scenario may benefit from several genetic counselling appointments and psychological support may be beneficial for those patients/couples expressing distress.

Genetic counselling may be performed either individually or in the presence of both members of the couple, depending on the nature of the result; couple-based counselling is particularly recommended for high-risk results, whereas individual counselling may be acceptable for low-risk results.

Finally, all information derived from a post-test genetic counselling appointment should be provided also in written form (e.g. in the form of educational materials, leaflets, a counselling letter or report) in order to enable patients to later consult these. By offering proper pre-test and post-test genetic counselling, patients may make fully informed decisions, thus deriving maximum benefit from ECS. Several studies have shown that based on ECS results, couples may adapt their reproductive planning, hence showing the clinical utility of ECS (Beauchamp et al., 2019, Capalbo et al., 2021, Ghiossi et al., 2018, Johansen Taber et al., 2019).

It should be noted that one of the main barriers when considering genetic counselling is the economic burden and lack of availability of trained genetic counsellors or clinical geneticists. For pre-test counselling, alternatives such as informative videos, websites or leaflets have been explored. As artificial intelligence tools, including large language models (LLMs) and chatbots, become increasingly used in clinical genetics for tasks such as answering patient queries, simplifying informed consent documents, and supporting clinical workflows, it is essential that their use is transparent (Duong and Solomon, 2025). Providers must inform patients when a chatbot or LLM is involved, explaining the tool's purpose, its capabilities, and its limitations. Healthcare professionals should guide patients through each step of the procedure, ensuring comprehension of what data will be used, how results will be communicated, and who will be responsible for follow-up, and be available to address questions the AI tool does not resolve (Duong and Solomon, 2025). Enhancements in program-specific accuracy, data privacy, model

performance in diverse populations, and clinical oversight must be maintained at all times to ensure safe, equitable, and responsible deployment (Coen et al., 2025).

For more routine and low-complexity sessions (such as pre-test counselling or low-risk post-test counselling) less specialised professionals may assist in providing some basic genetic counselling (Kirk et al., 2024). In this context, the emerging role of the genetic counselling assistant may play an essential role (Hnatiuk et al., 2019, Pirzadeh-Miller et al., 2017). Some studies have also explored the utility of reproductive aids to reinforce these low-complexity genetic counselling sessions (such as chatbots, videos or Artificial Intelligence agents) (Chavarri-Guerra et al., 2025, Coen et al., 2025, McDaniels et al., 2020, Nazareth et al., 2021). Under no circumstances should the molecular report of ECS replace post-test genetic counselling. Additionally, any high-risk results, IFs or patients demanding more detailed information should be referred to a professional specialising in genetic counselling (ideally a genetic counsellor, where the profession exists).

Recommendations

Post-test counselling should be mandatory for the at-risk couples and individuals with a positive result.
Post-test counselling should be recommended for couples at low risk. Other pathways are acceptable, given that these are validated.
Post-test genetic counselling should deliver result-specific guidance tailored to the level of risk, and including clinical implications, residual risk, emotional impact, family communication, and reproductive options.
Referral to appropriate specialist care should be ensured in cases of high-risk results or clinically significant incidental findings.
Genetic counselling may be performed either individually or in the presence of both members of the couple, depending on the nature of the result; couple-based counselling is particularly recommended for high-risk results, whereas individual counselling may be acceptable for low-risk results.

Informed consent

Respecting autonomy means any individual going through ECS, both patients and donors, must give informed consent, understanding the purpose, nature, and potential impact on themselves - and close family members - of the test (Dondorp et al., 2014). All information contained in the pre-test and post-test genetic counselling sessions should be clearly specified in the informed consent to acknowledge full understanding (Table 3).

Table 3. Core elements required in an informed consent form for ECS.

Aspect of informed consent	Key elements	Reference(s)
Voluntariness and autonomy	ECS is optional, and both patients and gamete donors should autonomously accept testing.	
Health implications and carrier status	It is essential that both patients and donors understand that their carrier status will not, in most cases, impact their health, but might affect their own reproductive choices.	
Incidental findings	If IFs may be reported, this should clearly be specified in informed consent, and patients given the option to opt-out of such findings.	
Scope and complexity of ECS panels	ECS for a high number of conditions poses further significant challenges to achieving meaningful informed consent, as specific details for all the conditions screened for may not be feasible. Alternatively, the inclusion and exclusion criteria for genes/disorders can be discussed.	
Test limitations and residual risk	Patients need to know and understand the limitations of ECS and be made aware of residual risks of the test.	
Donor-recipient matching	When matching donors and recipients based on carrier status or risk profiles, recipients must also consent and acknowledge the residual risks involved.	
Genetic counselling	Specialised counselling from a genetics professional is essential for both donors and recipients to fully understand the implications of these processes.	(Dondorp et al., 2014)
Future analysis and recontact (donors)	For donors, if additional genes may be later analysed for matching purposes, this should be clearly specified in the consent form, and they should be given the possibility to recontact to be informed of any relevant findings.	

Recommendations

Informed consent should reflect full understanding of ECS's purpose, nature, benefits, limitations, and implications for the individual and family.
Donors should be able to receive their results; the consent form should also mention that donors can opt out of receiving their results.

Reproductive options

When ECS identifies an ARC for AR or XLR condition, a range of reproductive options become available depending on the mode of reproduction, with or without MAR, but here we will only discuss reproductive options in the context of MAR. The most appropriate course of action depends on multiple factors, including the couple's values, the clinical setting, and the specific condition identified—particularly in relation to its severity and potential impact (de Wert et al., 2021, Gregg et al., 2021, Henneman et al., 2016).

The actionability of a positive ECS result—defined as the proportion of ARCs who pursue reproductive strategies to mitigate the identified risk (e.g., PGT-M, PND, or the use of donor gametes)—is a key determinant of the test's clinical utility in reproductive medicine. These strategies are not limited to strictly preventive measures but may also support informed reproductive planning. Actionability also reflects the clinical relevance and design quality of the gene panel used, underscoring the importance of including conditions for which actionable outcomes are possible and supported by appropriate counselling and care pathways.

In general, the higher the proportion of ARCs who act upon a positive ECS result, the greater the clinical utility of the screening test and the more robust the gene curation process behind the development of the ECS panel. According to the published literature, when ECS identifies carrier status for severe to profound conditions, the majority of ARCs (>70%) choose to pursue active reproductive risk mitigation, either through PGT-M during IVF or via PND following natural conception (Franasiak et al., 2016, Ghiossi et al., 2018, Kirk et al., 2024). In contrast, when the identified condition is classified as mild, or is characterised by reduced penetrance and variable expressivity, the rate of change in reproductive planning is markedly lower (Ghiossi et al., 2018). This results in a diminished clinical utility of ECS in such contexts, highlighting the importance of careful gene selection and classification when designing screening panels. Among the available reproductive options, some ARCs may elect to proceed without intervention, accepting the reproductive risk based on the nature of the condition and their personal, ethical, or religious beliefs (Ghiossi et al., 2018). Some papers claim ARCs proceeding without intervention is a failure of ECS, however, proceeding without intervention is one of the reproductive options and therefore not a failure of the test. In a smaller subset of cases, the discovery of a high genetic risk may prompt more substantial changes in reproductive plans, including the use of donor gametes, adoption, or the decision to remain child-free, although few evidence/data exist on this (Cannon et al., 2019).

Although PGT-M may be more readily integrated into the MAR pathway, access and uptake vary and are shaped by clinical, financial, regulatory, and personal factors (Kirk et al., 2024).

The timing of testing can also significantly influence the reproductive options available to ARCs. When ECS is performed during an ongoing pregnancy, which is less likely but not excluded after MAR, ARC may choose to continue the pregnancy despite a positive prenatal result, particularly in cases where early medical intervention or management options are available for the detected condition.

In gamete donation cycles, significant differences exist that must be understood. Considering that ethnic background, in our multiethnic society, is often inaccurately self-reported (Edwards et al., 2015) and the growing trends of cross-border gamete donation, ECS provides donor selection policies that can be normalized with respect to the reproductive risk for recessive disorders (Mersha and Abebe, 2015). Therefore, ECS has become a valuable tool for identifying potential risks of transmitting genetic disorders that might not otherwise be predicted and

provides reassurance to prospective recipients (Retsinformation, 2015a, Retsinformation, 2015b).

Ultimately, the clinical value of ECS is determined by the availability of tangible reproductive choices based on risks identified. This underscores not only the importance of offering well-designed ECS panels in reproductive settings, but also the critical role of comprehensive pre- and post-test genetic counselling to support individuals and couples in navigating the resulting reproductive options. Notably, the actionability and clinical utility of ECS are influenced by legal, cultural, and socio-religious contexts. In countries where preconception genetic testing is both accessible and integrated into standard reproductive care—and where there are minimal religious or ethical constraints—ECS is likely to demonstrate greater clinical impact and utility.

Recommendations

It is recommended not to reject donors only based on their carrier status for an AR disease.
The recipient should be notified of reproductive options.
Constant monitoring and review of ACRs rates and reproductive decision outcomes is recommended to inform and improve ECS practice over time.

Ethical issues

The responsible implementation of preconception ECS in MAR, including in gamete donation, requires assessing the proportionality of such screening offers, i.e. if the possible benefits clearly outweigh the possible harms and disadvantages, while respecting basic rights and values. ESHRE's Ethics Committee comprehensively outlined the ethical issues raised by ECS in MAR and made a number of recommendations (de Wert et al., 2021). Previously, the ESHRE Task Force on Ethics and Law published recommendations on the use of genetic screening of gamete donors (Dondorp et al., 2014). This section summarises and combines the key points of these documents regarding specific issues, highlighting when recommendations might need to be added or reconsidered in light of recent developments in this rapidly moving field.

In reproductive genetic screening, a longstanding tension exists between autonomy, which prioritises informed reproductive choice, and prevention, which seeks to reduce the incidence of genetic conditions. The prevailing view is that the autonomy paradigm should guide universal ECS, with broad consensus that its primary aim is to support autonomous decision-making (Henneman et al., 2016).

ECS can enable reproductive autonomy

- To empower individuals and couples with informed reproductive choices.
- To facilitate timely reproductive interventions, particularly in the context of MAR.
- To improve carrier detection through ancestry-independent screening methodologies.

Although offering ECS exclusively to couples undergoing MAR may be seen as conflicting with the principle of non-discrimination, there are context-specific justifications for such a selective approach. Fertility specialists have an ethical obligation not only to support the health and well-being of the prospective mother but also to consider the welfare of the future child. Additionally, implementing ECS within the MAR population provides a structured opportunity to evaluate its clinical utility, feasibility, and psychosocial impact. Insights gained from this targeted implementation could be instrumental in shaping future policies for broader, more equitable ECS implementation (de Wert et al., 2021).

Nonetheless, individuals undergoing MAR constitute a particularly vulnerable group, and caution is warranted to prevent the undue commercial promotion—or "upselling"—of genetic tests. While it is ethically appropriate to inform prospective parents without known genetic risks about the option of ECS, they should not feel pressured to undergo testing on moral grounds, such as an implicit suggestion that doing so constitutes responsible or "good" parenting. Providers should also acknowledge and respect patients' right to decline testing, ensuring that such decisions do not lead to judgment, reduced support, or compromised access to care. However, where a couple is identified as at risk for a serious AR condition, it is arguably reasonable to expect that they consider preventive reproductive options if they wish to conceive through MAR.

When used in gamete donation, ECS has the potential to enhance the safety of donor conception for recipients and their future children. The importance of ECS in gamete donation is accentuated by the fact that single donor gametes are frequently used across several families, potentially amplifying the transmission risk of inherited genetic disorders.

If the carrier status of the donor selected by the recipients or the clinician/lab is available, recipients can be presented with the three following options: recipients could be a) informed of the donor's carrier status, b) only informed of the most frequent and severe pathogenic variant identified, or c) not informed about donor carrier status at all. If recipients are made aware of the donor's carrier status, measures to minimise the added uncertainty, anxiety, and financial burden it could place on recipients should be implemented, including through adequate counselling (Dondorp et al., 2014).

In line with principles of responsible clinical practice, recipients should also be offered the option of further testing, especially if the selected donor is a carrier of any pathogenic variants. Depending on context (origin of the donor, availability of the original tested panel), this could take the form of an expanded carrier panel, similar to that used with the donor, or a targeted 'matching test', which only tests the recipient for the pathogenic variant(s) carried by the donor. The latter ensures that recipients are not unnecessarily exposed to the full complexity and expense of extensive genomic panels, while still protecting the health of future children.

Recipients should be provided with information about the option cost and implications of undergoing complementary carrier test, including the existence of residual risks and the expectation that they may need to change donor if they also carry the same pathogenic

variant(s). However, recipients should have the option to decline the match test or any carrier test if they are unwilling or unable to undertake it. They should not feel pressured to undergo testing on moral grounds, such as an implicit suggestion that doing so constitutes responsible or "good" parenting. Providers should also acknowledge and respect patients' right to decline testing, ensuring that such decisions do not lead to judgment, reduced support, or compromised access to care. However, in such cases, recipients should sign a document acknowledging that they have been informed of the donor's carrier status and accept the potential risk of transmission.

Both in donation and in autologous conception, if a risk is identified after embryos are created, it is important to consider the implications it may have for the future donor-conceived child's wellbeing, and the option of PGT-M or prenatal testing should be discussed with the prospective parents.

Professionals, particularly in MAR settings, face ethical responsibilities beyond facilitating pregnancy. They are also tasked with considering the future child's welfare, including known genetic risks (de Wert et al., 2021, Pennings et al., 2007).

For low-risk couples, non-directive guidance is offered, allowing them to decide whether to undergo testing and how to proceed if they are at risk. For higher-risk groups, such as those with ancestry or family history linked risks, professionals may take a more directive approach, potentially making access to MAR conditional on reducing genetic risks (de Wert et al., 2021).

Ultimately, while the autonomy paradigm is dominant, concerns about the welfare of the future child can justify more directive approaches, especially when there is a significant risk of serious suffering. This nuanced approach aims to balance reproductive autonomy with ethical concerns about preventing harm to future children (de Wert et al., 2021).

This is also relevant in the context of gamete donation. However, when it comes to donors themselves, 'as all donors are carriers of AR conditions, extended carrier testing only makes sense if heterozygosity does not necessarily lead to exclusion. This requires that recipients are also tested, so as to allow matching of donors and recipients to avoid carrier combination' (Dondorp et al., 2014).

Recommendations

In MAR, ECS should be offered as a voluntary, non-directive screening test to patients without known genetic risks, and individuals should not be pressured to undergo testing or to act upon results.
Couple identified as carriers for a serious AR condition are expected to consider preventive reproductive options if they wish to conceive through MAR.
In gamete donation, if the carrier status of the donor is available, three options are available: recipients could be a) informed of the donor's carrier status,

b) only informed of the most frequent and severe pathogenic variant identified, or
c) not informed about donor carrier status at all.

If the recipients are made aware of the positive carrier status of their donor for a severe condition, they should be offered a ECS or match test, or the possibility to change donor, while receiving adequate counselling.

If the recipients refuse to take a match test or change donor, they should sign a waiver document. The patients' choice should be respected and not affect the care proposed.

General take-home messages for clinical implementation of ECS in MAR

ECS is increasingly recognised as a valuable component of reproductive care, with particular relevance in MAR. ECS enables informed reproductive decision-making and supporting a range of risk mitigation strategies. Its clinical value, however, depends not only on technological capability but also on careful integration within robust ethical, clinical, counselling, and laboratory frameworks. This Good Practice Recommendations document addresses a critical gap by providing MAR-specific guidance for ECS, including gamete donation. It responds to the substantial heterogeneity observed across current practices (Capalbo et al., 2024)(Herbrand et al., 2026) and professional recommendations by articulating core principles for eligibility, timing, panel design, result interpretation, counselling, and ethical governance. Central to these recommendations is the recognition that ECS is a screening tool aimed at identifying reproductive risk, rather than a diagnostic test, and that its primary objective is to support reproductive autonomy through informed choice.

ECS in the broader framework of reproductive care

ECS should be considered within a broader framework and evaluated alongside other screening and testing tools used throughout the reproductive pathway such as prenatal testing and newborn screening. Newborn screening aims to identify affected infants shortly after birth in order to enable early diagnosis and treatment, whereas ECS is performed prior to conception or early in pregnancy with the explicit goal of informing reproductive planning. The two programs are therefore complementary rather than interchangeable, addressing distinct clinical questions at different stages of the reproductive pathway. Some examples of shared conditions between the two screening programs, illustrating their complementary roles, include cystic fibrosis and spinal muscular atrophy. When these conditions are included in ECS panels, they allow early identification of at-risk couples and access to meaningful reproductive options, while their inclusion in newborn screening enables early postnatal disease management. By contrast, conditions that are primarily included in newborn screening because early detection enables timely intervention and favourable clinical outcomes, and for which reproductive decision-making is unlikely to be significantly influenced (e.g., phenylketonuria, congenital hypothyroidism) offer little or no added value when included in ECS panels. These distinctions highlight that overlap between ECS and newborn screening should be guided by reproductive utility rather than by diagnostic detectability alone. The working group considers it appropriate to include gene–disease pairs irrespective of their presence in newborn

screening programs when this provides additional reproductive benefit such as carrier identification before pregnancy or informing decisions regarding preimplantation genetic testing, prenatal diagnosis, or donor selection. ECS should not be viewed as a substitute for newborn screening, nor should the existence of newborn screening programs be used to justify restricting ECS where reproductive benefit can be demonstrated.

Similarly, ECS is complementary to other screening tests used during pregnancy to assess different categories of genetic risk, such as non-invasive prenatal testing (NIPT) for common aneuploidies. The widespread adoption of NIPT in Europe where it is increasingly offered as a first-tier screening test for the general pregnant population, has transformed the landscape of reproductive genetics (Van Den Bogaert et al., 2021, van der Meij et al., 2019). However, owing to the low sequencing depth of maternal plasma DNA, accurate detection of maternal carrier status for single-gene conditions is currently not feasible. From a clinical perspective, ECS can still be offered during pregnancy, alongside NIPT for aneuploidy screening. Nevertheless, the working group emphasises that offering ECS prior to conception remains the preferred approach, as it maximises the reproductive options available to prospective parents. In the context of MAR, where patients are already engaged in structured reproductive care pathways such as IVF, implementing ECS before treatment initiation represents a particularly feasible and clinically valuable strategy.

ECS in gamete donation

ECS also plays an important role in the context of gamete donation, where genetic matching between donors and recipients may help minimise the risk of transmitting recessive conditions while avoiding unnecessary exclusion of donors based solely on carrier status. Implementing structured donor–recipient matching strategies may therefore support both reproductive safety and donor availability within MAR programs. For these reasons, the working group strongly recommends that donors should not be excluded solely on the basis of carrier status for autosomal recessive conditions.

ECS and health care economics

From a health-economic perspective, ECS has the potential to be cost-effective, particularly when implemented prior to conception and integrated into existing MAR pathways. By identifying at risk couples before embryo creation or pregnancy, ECS may reduce downstream costs associated with the diagnosis, treatment, and long-term care of severe genetic conditions, as well as the emotional and clinical burden of late diagnoses. Cost-effectiveness is influenced by multiple factors, including panel design, carrier frequency thresholds, counselling models, uptake rates, and the availability of actionable reproductive options such as PGT-M or donor matching. Importantly, broader panels are not inherently more cost-effective; clinical utility depends on the careful selection of conditions for which meaningful reproductive decisions can be made (Busnelli et al., 2023).

Several studies across different healthcare systems have demonstrated the cost-effectiveness of ECS. Analyses conducted in U.S. health plans, private insurance settings, and universal healthcare systems have consistently shown that ECS reduces affected births and healthcare costs compared with limited carrier screening or no screening strategies (Azimi et al., 2016, Beauchamp et al., 2019, Busnelli et al., 2023, Zhang et al., 2019). More recently, a large microsimulation study in Australia confirmed that population-based expanded reproductive carrier screening is cost-saving compared with both limited panels and intermediate sized screening strategies, with higher quality-adjusted life-years and substantially more affected births averted even at moderate uptake levels (Schofield et al., 2025).

Different reporting strategies may also influence the clinical implementation of ECS. Both individual carrier reporting and couple-based risk reporting represent valid approaches, and the choice between them may depend on available counselling resources, clinical workflows, panel design, and national regulatory frameworks. In general, the working group considers that communication of individual carrier results should be preferred whenever feasible. Providing individual results allows carriers to be informed about their own genetic status, which may have implications beyond the current reproductive partnership and may facilitate cascade testing in family members. However, the working group also recognises that when ECS panels include a very large number of genes, individual reporting may generate a substantial amount of information and may increase the counselling burden for both patients and healthcare professionals. In such situations, couple-based reporting may represent a pragmatic alternative. Appropriate mechanisms should remain available to ensure that individuals can access their own carrier information if clinically relevant or upon request.

Laboratory considerations and program evaluation

From a laboratory perspective, cost-effectiveness is closely linked to evidence-based panel design, transparent gene selection, and robust variant interpretation frameworks. Continuous panel re-evaluation, quality assurance, and harmonisation across laboratories are essential to ensure clinical validity and sustainable implementation. The increasing availability of large, multi-ancestry population biobanks in Europe and beyond, such as UK Biobank, Estonian Biobank, All of Us, and FinnGen, together with advances in variant annotation frameworks and computational interpretation tools (such as AlphaGenome, PopVEP, Evo2) provide a rapidly expanding infrastructure to support the refinement and implementation of ECS while improving analytic accuracy, clinical validity, and consistency of results. Finally, the long-term value of ECS in MAR will depend on ongoing evaluation of clinical outcomes, at-risk couple detection rates, reproductive decision-making and equity of access. Monitoring these parameters will be essential to refine practice, inform reimbursement and funding models, and guide future policy development at national and international levels.

ECS and genetic counselling

Appropriate genetic counselling remains central to the responsible and cost-effective implementation of ECS. High quality pre- and post-test counselling supports informed decision making, mitigates psychological harm, and reduces the risk of misinterpretation or unnecessary follow-up testing. While digital tools and alternative counselling models may help address workforce constraints and have been validated in other branches of genetics (Yi et al., 2025) (Yi et al., 2025), they cannot replace professional responsibility, particularly for high-risk results, IFs, or complex reproductive decisions. At the same time, the working group recognises that the availability of genetic counselling services may represent a practical barrier to the broader implementation of ECS programs. For this reason, the group considers it acceptable to explore alternative models that help mitigate this burden, in particular for low-risk couples.

These recommendations should be interpreted in light of several limitations. The evidence base supporting ECS continues to evolve, and many aspects of ECS implementation including optimal panel composition, counselling models, and reporting strategies, remain areas of active debate. As a Good Practice Recommendations document, this reflects expert consensus informed by available literature and current clinical practice rather than formal evidence grading for all recommendations. Furthermore, healthcare systems across Europe and internationally differ substantially in terms of funding models, regulatory frameworks, and access to genetic services. Consequently, local adaptation may be required to ensure that ECS implementation remains feasible, proportionate, and aligned with national policies.

Technical considerations, technological approaches and future directions

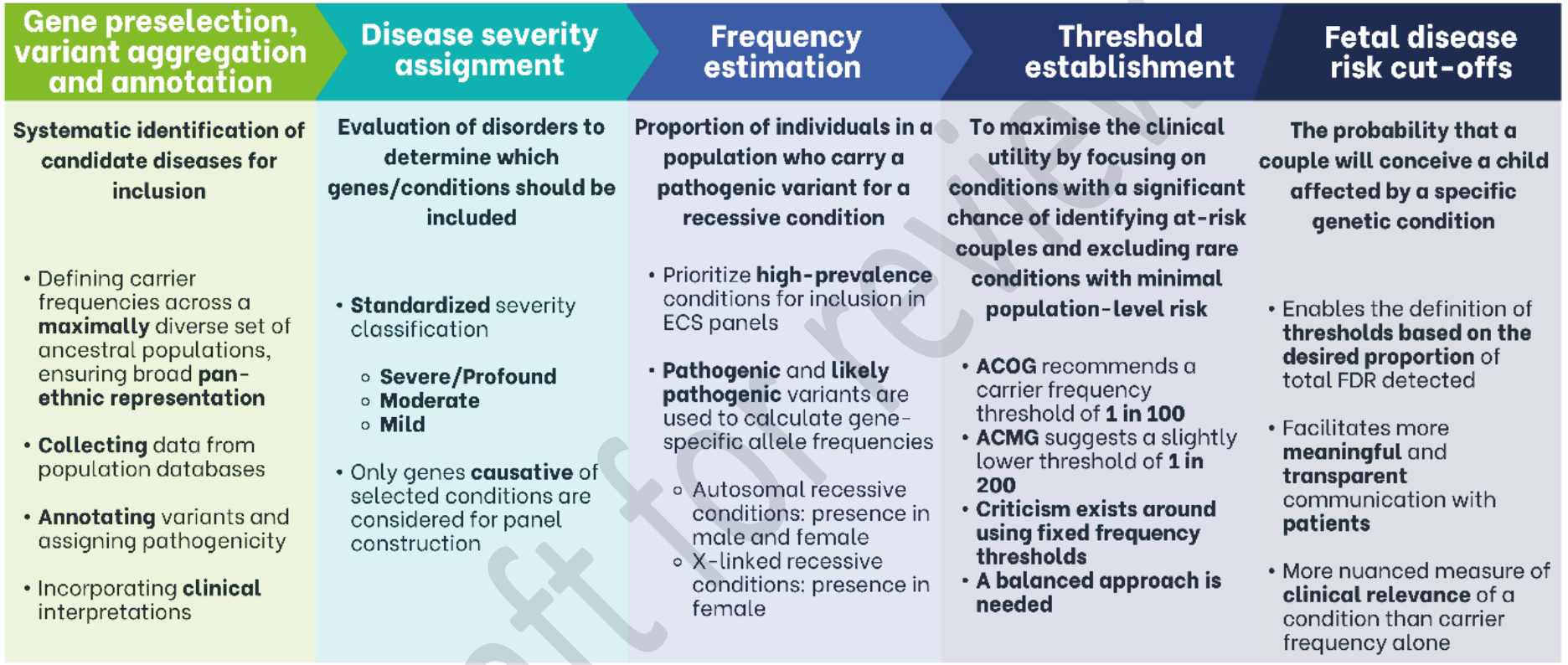
ECS panel design

The design and implementation of an evidence-based ECS panel involves critical steps from selecting relevant disorders to ensuring accurate variant detection and test clinical utility.

The development of an ECS panel should follow a structured and methodologically transparent workflow; however, the sequence of individual steps may vary according to the clinical context, population characteristics, and resource availability. Accordingly, the framework outlined below should be regarded as a guiding approach that highlights key considerations in ECS panel design rather than a prescriptive sequence.

Two general approaches may be applied. In a clinical-first approach, diseases are first preselected based on predefined inclusion criteria, followed by an estimation of population carrier frequencies for the associated genes. A final gene list is then curated using an established carrier frequency threshold (Gregg et al., 2021, Gruzin et al., 2025, Johansen Taber et al., 2022). Alternatively, in a data-driven approach, laboratories may initially determine carrier frequencies for genes associated with recessive conditions and subsequently evaluate the severity of the associated disorders for inclusion in the panel (Schmitz et al., 2025).

828 *Figure 1. Overview of the framework for selecting conditions in expanded carrier screening (ECS), including gene selection and annotation, frequency estimation, threshold setting, disease severity*
829 *classification, and fetal disease risk assessment.*



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Selection of eligible conditions and genes

The design of an ECS panel requires the systematic identification of candidate conditions and associated genes for inclusion. This process involves a comprehensive evaluation of disorders with established autosomal recessive and X-linked inheritance, drawing on curated databases such as Online Mendelian Inheritance in Man (OMIM) and ClinGen and evidence from published literature and existing carrier screening frameworks (Gregg et al., 2021, Guo and Gregg, 2019, Kirk et al., 2021).

Gene selection should be guided by clearly defined and transparent criteria to ensure consistency across laboratories. These criteria should aim to balance clinical utility, ethical considerations, and technical feasibility, while supporting meaningful reproductive decision-making for individuals and couples.

The key gene inclusion criteria for ECS panels are as follows:

1) Disease severity

Disease severity is a central consideration in ECS panel design; however, it is inherently subjective and may vary depending on clinical context, cultural perspectives, and patient values (Freeman et al., 2025). To maintain transparency and reproducibility in panel design, it is recommended to adopt standardised severity classification frameworks. Relevant parameters include age of onset, impact on cognitive and physical functioning, effect on lifespan, and the availability of effective treatments or interventions. One widely referenced framework is the severity classification algorithm developed by Lazarin *et al.* (2014), which stratifies conditions into four categories - profound, severe, moderate, and mild - based on phenotypic and clinical data. This framework has been used by several ECS programs and provides a practical foundation for systematic disease categorisation (Gregg et al., 2021, Lazarin et al., 2014).

- Severe and profound disorders are characterised by a detrimental impact on quality of life, including significant cognitive or physical impairment, substantially shortened lifespan, or both. These conditions represent the core target of ECS and are universally recommended for inclusion. Examples include Tay-Sachs disease (HEXA), spinal muscular atrophy (SMN1), and Canavan disease (ASPA) (ACOG, 2017a, Gregg et al., 2021).
- Moderate disorders may involve chronic disability or functional limitation but are not typically associated with significantly shortened lifespan. Their inclusion in ECS panels is generally supported when they are associated with meaningful reproductive impact or when identifying carrier status would substantially inform reproductive decision-making. Nonsyndromic hearing loss (e.g., GJB2-related) is a commonly cited example, though its inclusion remains a subject of debate given the variability in how the deaf community perceives hearing loss as a disability (Freeman et al., 2025).
- Mild disorders – those with minimal clinical impact, high manageability with standard medical care, adult onset, low penetrance, or significant variable

expressivity - should generally not be included in ECS panels. Their inclusion risks causing disproportionate patient anxiety, may compromise the clinical actionability of results, and can dilute the reproductive utility of the panel. For example, HFE-related hereditary haemochromatosis, despite being relatively common, is characterised by low penetrance and is manageable with routine monitoring and phlebotomy; it is therefore excluded from most professional ECS panels (ACOG, 2017a, Allen et al., 2008).

It is important to acknowledge that applying severity classifications is not always straightforward. While the primary goal of an ECS panel is to identify carrier status for severe and moderate childhood-onset conditions, the inclusion of certain genes inevitably introduces a spectrum of phenotypic expression, ranging from mild to profound, as a consequence of significant allelic and phenotypic heterogeneity. For instance, variants in genes such as CFTR (cystic fibrosis transmembrane conductance regulator) are associated with a broad phenotypic spectrum, from classic multisystem cystic fibrosis to isolated congenital bilateral absence of the vas deferens (CBAVD), a mild, fertility-related condition in males (Brennan and Schrijver, 2016). Where relevant, information on the range of phenotypes associated with particular genes should be provided, and post-test counselling should adequately address this complexity.

ECS is increasingly implemented as a pan-ethnic screening approach, which avoids reliance on self-reported ancestry and promotes equitable access to genetic screening. However, differences in carrier frequency across populations remain clinically relevant and should be considered in panel design and interpretation. A population-based study in Singapore demonstrated that several genes associated with severe paediatric-onset conditions such as ADAR, CYP7B1, DDC, GALC, LAMA3, SBDS, and SPINK5 may reach carrier frequencies exceeding 1 in 200 in specific Asian populations despite not being consistently included in widely used ECS panels, including those based on ACMG recommendations (Bylstra et al., 2025). Conversely, some conditions are highly prevalent in particular ancestry groups but rare or absent in others; for example, Friedreich ataxia, caused by variants in FXN, has a carrier frequency of approximately 1 in 60 to 1 in 100 in individuals of European, Arab, and South Asian ancestry, but almost absent in sub-Saharan African and East Asian populations (Indelicato et al., 2025, Reetz et al., 2025).

These examples underscore the recommendation that carrier frequency thresholds should be evaluated across multiple ancestral groups using population-specific genomic data to ensure that panel design remains equitable and clinically meaningful across diverse populations (Bylstra et al., 2025, Gregg et al., 2021). It should additionally be noted that the potential relevance of certain conditions beyond their primary reproductive purpose has been discussed in the literature; however, this remains debated and should be carefully weighed against the primary purpose of ECS as a tool for reproductive risk assessment and informed decision-making (Henneman et al., 2016).

2) Gene-disease relationship

The strength of evidence supporting the relationship between a gene and its associated disease is a critical determinant of inclusion in an ECS panel. Only genes with well-established, clinically validated associations should be included; the incorporation of genes with insufficient or conflicting evidence risks generating uncertain or misleading results that cannot support accurate reproductive risk counselling.

It is recommended that gene-disease relationship (GDRs) are evaluated using structured, evidence-based frameworks. The ClinGen Gene-Disease Validity framework provides a rigorous and internationally recognised approach, classifying GDRs with supporting evidence as definitive, strong, moderate, or limited based on a systematic review of genetic and experimental evidence (Strande et al., 2017). For ECS panels, inclusion should generally be restricted to genes classified as having definitive or strong evidence of causality; genes with moderate evidence may be considered on a case-by-case basis, particularly in the context of emerging gene-disease associations or genetically heterogeneous conditions, provided their inclusion is justified, clearly communicated to patients, and appropriately reflected in the reporting framework. Genes with limited, disputed, or refuted classifications should be excluded.

Evidence within this framework is evaluated across two broad domains:

- Genetic evidence encompasses case-level data, including reports of multiple unrelated probands harbouring pathogenic variants consistent with the associated phenotype, de novo variant occurrences, and predicted or proven null variants, as well as segregation data within families, and case-control studies demonstrating statistically significant enrichment of variants in affected individuals compared to controls. The framework applies a structured scoring system to weight the quality and quantity of this evidence, taking into account variant type, inheritance pattern, and population frequency data.
- Experimental evidence includes gene-level functional data supporting biological plausibility of the gene–disease association. This encompasses biochemical function studies, protein interaction data, expression analyses in disease-relevant tissues, functional alteration studies in patient-derived or non-patient cells, and model system data from animal or cell culture models demonstrating a phenotype consistent with the human disease. Rescue experiments, in which re-introduction of the wild-type gene product reverses the model phenotype, provide particularly strong supportive evidence.

Panels should be subject to regular review and updating as new evidence emerges, and curated resources such as ClinGen, OMIM, and Orphanet should be checked to ensure that GDR classifications remain accurate.

3) Technical feasibility and analytical accuracy

The inclusion of genes in ECS panels should be contingent upon the ability of the testing platform to reliably detect clinically relevant variants. Analytical validity must be demonstrated for variant types of interest, including single-nucleotide variants, small insertions/deletions, and, where appropriate, copy number variants or complex genomic rearrangements.

Certain genes pose technical challenges due to factors such as pseudogene homology, repetitive sequences, or structural complexity. These genes should only be included where validated methodologies ensure high analytical sensitivity and specificity. For example, SMN1 gene cannot be reliably analysed by standard short-read sequencing alone due to the presence of a highly homologous pseudogene (SMN2), and therefore requires dedicated methods such as copy number-based assays for accurate assessment (Feng et al., 2017, Scarciolla et al., 2006). Consideration should also be given to detection rates, assay limitations, and the ability to accurately interpret detected variants within a clinical context.

In summary, the inclusion criteria should prioritise genes with well-defined reproductive significance based on disease severity, validated gene-disease associations, and technical feasibility, providing a transparent and balanced basis for gene selection.

Determining Variant Carrier Frequency

Once the initial gene list has been established, the next critical step is to determine variant carrier frequencies (VCF), ideally, across a broad and ancestrally diverse set of populations. This ensures that the panel reflects pan-ethnic representation rather than being skewed towards specific groups. Traditional carrier screening panels often relied on self-reported ancestry, but this approach is now recognised as inadequate due to the high degree of admixture observed in human populations. In fact, ancestry-based testing consistently underestimates the number of carriers, potentially missing ARCs (ACOG, 2017a, Sagaser et al., 2023).

For the purpose of VCF calculations, variant aggregation and annotation is performed as described below:

1) Variant aggregation

Allele frequency corresponds to the proportion of a given allele (variant of a gene) at a specific locus relative to the total number of alleles in the population. Extraction of allele frequency data from large-scale variant repositories is crucial for VCF estimation. Resources such as the Genome Aggregation Database (gnomAD), the UK Biobank, the All of Us Research Program, and national or institutional biobanks provide allele frequency data across global populations, including admixed groups, thereby reducing the biases inherent in ancestry-specific approaches (Bylstra et al., 2025, Gregg et al., 2021, Schmitz et al., 2025). Incorporating both publicly available and proprietary or institutional databases improves accuracy and allows laboratories to account for rare or population-specific variants that may not be represented in public resources alone. This is particularly relevant for XLR conditions, where low prevalence

requires very large cohorts to obtain reliable estimates. For example, for an XLR condition with a male prevalence of approximately 1 in 40,000, the expected carrier frequency in females is around 1 in 20,000, meaning that small sample sizes are unlikely to yield stable or precise VCF estimates; such estimates should therefore be interpreted with caution and supported by large genomic datasets and robust external epidemiological data. Of note, it is essential to consider the characteristics of each gene when deriving variant frequency data. For technically challenging genes (e.g. due to structural nature of variants) such as *CYP21A2, FMR1*, and *SMN1*, exome- and genome-based databases (e.g., gnomAD) often lack accuracy, and sources employing validated supplementary methods to assess these genes (e.g., multiplex ligation-dependent probe amplification (MLPA), quantitative polymerase chain reaction (qPCR), triplet-primed PCR (TP-PCR)) should instead be used.

2) Variant annotation and pathogenicity assessment

Variants identified through data aggregation must be systematically annotated and classified to determine their clinical relevance for carrier frequency estimation. The ACMG/AMP guidelines provide the internationally recognised framework for classifying variants into five tiers: pathogenic (P), likely pathogenic (LP), variant of uncertain significance (VUS), likely benign (LB), and benign (B), based on a structured assessment of multiple evidence types, including population data, computational data, functional data, and segregation data (Richards et al., 2015). In the ECS context, only P/LP variants are used to derive carrier frequency estimates, making the rigour and consistency of this classification process directly consequential for panel accuracy. Population frequency data from large-scale databases such as gnomAD inform key criteria, including PM2 (absence or extreme rarity in population controls) and BA1 (stand-alone benign classification for variants exceeding 5% allele frequency) while variant type and location determine whether high-weight criteria such as PVS1 apply for loss-of-function variants in relevant genes (Richards et al., 2015). For missense variants, in silico tools including REVEL, CADD, and AlphaMissense contribute supporting computational evidence, though they should not be used as the sole primary classifiers (Cheng et al., 2023, Richards et al., 2015). Case-level evidence such as observation in multiple unrelated affected individuals, cosegregation data, and detection in trans with a known pathogenic variant (PM3), alongside functional data from validated assays, further inform final classification (Brnich et al., 2019). Curated resources including ClinVar, LOVD, and locus-specific databases such as CFTR2 should be consulted to capture expert-reviewed interpretations beyond automated annotation pipelines. Disease- and gene-specific ClinGen Expert Panel specifications have been instrumental in refining how individual evidence criteria are applied and weighted for particular conditions, improving classification consistency (Rivera-Muñoz et al., 2018). In addition, many laboratories maintain internal classification systems informed by historical case data, functional studies, and ongoing reclassifications. These internal resources are especially valuable for resolving VUS and for capturing knowledge that may not yet be publicly available. As variant classification is not static, laboratories should maintain robust workflows for periodic re-evaluation of variant classifications as new evidence emerges and existing classifications are updated.

Together, these steps ensure that variant aggregation and annotations provide accurate P/LP VCF estimates of gene carrier frequency (GCF). By combining large-scale data aggregation, standardised annotation, and curated clinical expertise, carrier screening panels can achieve both clinical validity and equitable representation across populations.

Calculation of Gene-specific Carrier Frequencies (GCF)

Gene carrier frequency (GCF) in the context of ECS represents the proportion of individuals in a population who carry a pathogenic/likely pathogenic variant for a recessive condition. Estimating GCF is crucial for assessing a condition's contribution to population-level risk. Accurate GCF estimates help prioritise high-prevalence conditions for inclusion in ECS panels, thereby enhancing sensitivity and clinical validity. After variant aggregation and curation, only pathogenic and likely pathogenic variants are used to calculate gene-specific allele frequencies. Well characterised variants with low penetrance or a mild phenotype should be excluded from this analysis.

For AR conditions, carrier frequencies are calculated by identifying the proportion of individuals, both male and females, who carry one copy of a P/LP variant (heterozygous). Allele frequency corresponds to the proportion of a given pathogenic allele at a specific locus relative to the total number of alleles in the population. These metrics can be used to estimate the probability of an ARC, which is approximately the square of the carrier frequency. For X recessive conditions, carrier frequency is typically calculated using female data, as females can be heterozygous carriers, whereas males with pathogenic variants are presumed to be affected and thereby not seeking carrier screening.

Finally, estimates must also account for technical and methodological limitations. Differences in sequencing coverage, variant calling pipelines, and annotations can influence frequency estimates across datasets. Aggregation of data from various methods and cross-validation with multiple sources (e.g., gnomAD, biobank cohorts, and internal laboratory data) increases confidence in the final frequencies used to guide gene inclusion.

Panel design guided by Fetal Disease Risk (FDR)

Once population-level GCFs have been established for a preselected list of severe and moderate conditions, quantitative thresholds, based on cumulative carrier frequency and fetal disease risk (FDR), can be applied to define the final gene list. FDR represents the probability that a couple will conceive a child affected by a specific genetic condition on the screening panel. The overarching aim is to maximise clinical utility by prioritising conditions where there is a meaningful probability of identifying ARCs, whilst avoiding the inclusion of conditions so rare that their contribution to population-level reproductive risk is negligible.

Two broad approaches currently exist:

- Applying formal carrier frequency (and/or FDR) thresholds to define panel boundaries, as recommended by major professional societies (ACMG and ACOG). ACOG currently recommends a threshold of 1 in 100, meaning that conditions with a carrier frequency

equal to or greater than 1 in 100 are suitable for carrier screening. The ACMG, on the other hand, supports a slightly lower threshold of 1 in 200 in any ethnic group with a meaningful representation in the U.S. population.

- Adopting broader clinically curated panels without a defined carrier frequency cut-off (Kirk et al., 2021)(BeGECS genetic carrier screening program).

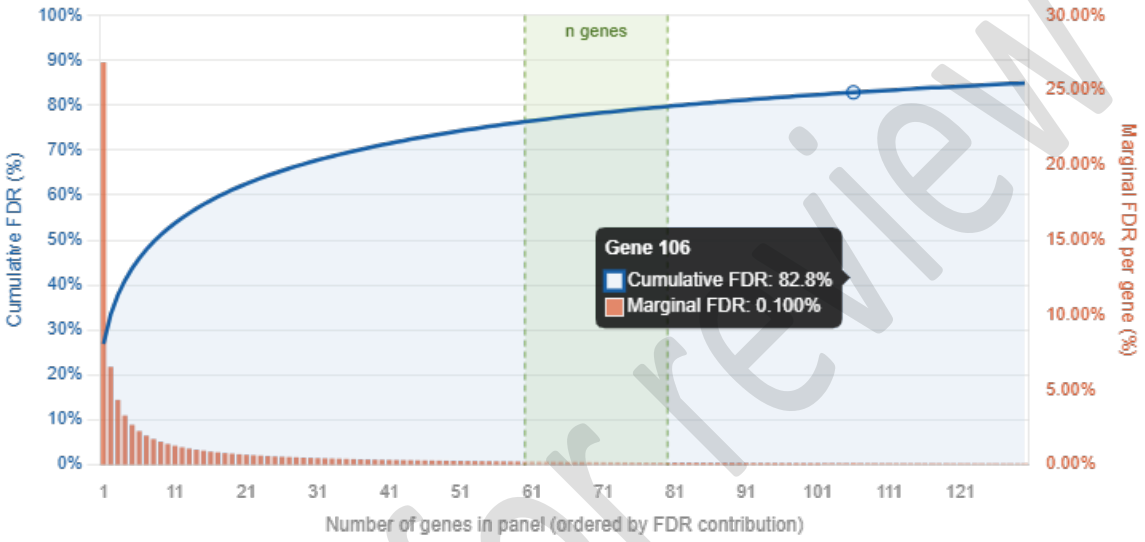
Both have merit and trade-offs, and the choice should be guided by clinical context, available resources, and healthcare system infrastructure.

If the panel design starts with the preselection of genes, it is recommended that the initial candidate list be as comprehensive as possible, capturing all severe and moderate childhood-onset conditions meeting the gene selection criteria described in the preceding sections, including disease severity, gene-disease relationship strength, and technical feasibility; irrespective of carrier frequency at this stage. Premature exclusion solely on frequency grounds risks omitting conditions of genuine reproductive significance, particularly those relevant to specific ancestral populations (Ben-Shachar et al., 2019, Schmidtke and Krawczak, 2022). It is therefore recommended that the initial candidate list capture, at a minimum, all conditions with a GCF of 1 in 200 in at least one ancestral population with meaningful representation in the screened cohort, consistent with ACMG Tier 3 guidance (Gregg et al., 2021). This represents a floor rather than a ceiling and conditions with lower carrier frequencies should not be automatically excluded where disease severity and gene–disease evidence are compelling; their ultimate inclusion should be determined by FDR analysis. Real-world implementation of the ACMG Tier 3 panel has demonstrated a clinically meaningful ARC rate of approximately 1 in 29, with the panel estimated to account for over 90% of the autosomal recessive disease burden in unrelated non-Finnish European populations (Schmidtke and Krawczak, 2022). It is nonetheless acknowledged that broader panels without formal frequency cut-offs can substantially increase ARC detection yield further: Mackenzie's Mission, which applied no carrier frequency threshold and screened over 1,300 genes, identified 1.9% of couples as at increased risk (Kirk et al., 2024, Kirk et al., 2021). Notably, retrospective analysis of the Mackenzie's Mission dataset demonstrated that applying the ACMG-recommended gene list to that cohort would have missed approximately 42% of at-risk couples identified through the broader panel, underscoring the yield limitations inherent to threshold-based approaches (Kirk et al., 2024). Such broader approaches, however, demand considerable investment in variant curation, counselling, and reporting infrastructure (Archibald et al., 2022). Given the trade-offs inherent to both approaches, an alternative pragmatic approach is to apply cumulative FDR analysis to a broad preselected gene list in order to define a final panel that captures the vast majority of population-level reproductive disease while remaining aligned with the resources available for its responsible implementation.

Foetal disease risk thresholds

FDR is calculated by integrating the carrier rates (CR) of both partners along with the mode of inheritance - for example, for AR conditions, FDR is estimated as (CR × CR) / 4, and for XLR conditions as CR_female / 4 (Haque et al., 2016). This information can be presented

cumulatively, beginning with conditions contributing the highest individual FDR and adding successive conditions in descending order of contribution. In most major ancestral groups with substantial genomic data available, the cumulative FDR typically reaches a plateau after including approximately 150 to 248 genes (Gruzin et al., 2025). This reflects a saturation point beyond which the marginal gain in additional disease risk captured is minimal. This saturation point will vary across populations and should, where possible, be evaluated separately for each target population. Laboratories and healthcare providers can choose a relevant FDR threshold (informing number of genes in a panel) to balance operations capabilities and costs along with the preferences of individuals undergoing carrier screening.



This approach facilitates more meaningful and transparent communication with patients, providing a clearer understanding of diagnostic yield and residual risk than methods based solely on arbitrary carrier rate cutoffs. The FDR metric provides a more nuanced measure of clinical relevance of a condition than carrier frequency alone. For instance, two conditions may have similar carrier rates but vastly different FDRs due to inheritance patterns.

It is recommended that gene lists are not treated as static. Panels should be subject to systematic review at a minimum of every two to three years or more frequently as new evidence emerges, with governance structures in place (e.g., defined review processes and documentation) to manage additions, removals, and reclassifications in a timely and transparent manner (Goldberg et al., 2023, Kirk et al., 2021).

Recommendations

ECS panel design should follow a structured, transparent, and evidence-based process.
Laboratories may adopt either a clinical-first or data-driven approach, depending on clinical context and available resources.
Panels should prioritise severe and profound childhood-onset conditions; moderate conditions may be included where they have a meaningful impact on reproductive decision-making.
Mild, low-penetrance, or adult-onset conditions should not be included.

Only genes with well-established gene–disease relationships should be included, based on structured evaluation frameworks. Genes with limited or conflicting evidence should not be included.
ECS should be implemented as a pan-ethnic screening approach. Differences in carrier frequency across populations should be considered, and population-specific adaptations may be applied where justified.
Gene carrier frequency estimates should be derived from datasets with adequate sample size, appropriate population representation, and robust methodological quality. Where feasible, multiple independent data sources should be used.
Laboratories should meet established best-practice standards, including use of validated public variant databases, explicit acknowledgment of gene-specific technical limitations, and the application of confirmatory methods where appropriate.
ECS panels should be regularly reviewed and updated, with transparent processes for the addition or removal of conditions.

Laboratory Techniques and Assay Design: Sequencing and orthogonal Methods

ECS relies on a combination of molecular methods designed to detect clinically actionable variants across a broad range of genes associated with AR and XLR disorders. Modern laboratory workflows integrate HTS, targeted variant detection, and orthogonal/ supplementary confirmation strategies to achieve high analytic sensitivity and clinical validity (Table 4). The selection of laboratory techniques depends on the variant type, gene structure, and laboratory throughput. Since there are multiple types of disease-causing variants, including single-nucleotide substitutions, insertions/ deletions, copy number changes, gene conversions, repeat expansions, and structural variants; it is challenging for a single molecular technique to capture all types of variants. Laboratories therefore use a combination of molecular methods and bioinformatic pipelines in validated clinical workflows. The 2024 ACMG technical standard outlines minimum methodological expectations for laboratories offering preconception and prenatal carrier screening and emphasises transparent reporting of assay scope and their respective limitations (Guha et al., 2024).

1. High-throughput sequencing

Short-read HTS remains the principal analytical platform for ECS due to its scalability, high throughput, and ability to interrogate dozens to hundreds of genes simultaneously. Within ECS workflows, HTS is used to sequence DNA libraries generated for either targeted gene panels (TGP), WES or, less commonly used, whole genome sequencing (WGS) (Satam et al., 2023, Slatko et al., 2018).

TGP are restricted to a predefined set of variants or full genes analysis and typically include coding exons with flanking intronic regions, though deeper intronic or regulatory regions may be included when clinically relevant. Sequencing libraries for TGPs are typically prepared using either amplicon-based enrichment or DNA hybridisation capture methods, enabling efficient coverage of targeted genomic regions, effective use of sequencing capacity, and reduced

computational burden. At sufficient depth of coverage, TGPs can demonstrate high analytical sensitivity for single-nucleotide variants (SNVs) and small indels within targeted regions. Nonetheless, detection accuracy may be reduced for copy-number variants (CNVs) and for technically challenging genomic regions, including those with high GC content or complex sequence structure. For these regions, orthogonal methods such as MLPA, Sanger sequencing, or qPCR are often required, to maintain high clinical sensitivity across all relevant variant classes within the targeted genes. A key limitation of TGPs is their fixed content: incorporating newly emerging disease genes or clinically relevant variants often requires redesigning capture probes or amplicons and extensive wet-lab redevelopment and validation. As clinical evidence evolves, this rigidity constrains rapid assay updates and precludes retrospective analysis of genes not originally included, limiting flexibility compared with broader sequencing approaches such as WES or WGS.

As sequencing costs continue to decrease and analytical pipelines evolve, WES and WGS offer broader and more flexible alternatives for ECS. In current clinical practice, WES is more widely adopted for ECS because it focuses sequencing of protein-coding regions, where most known disease-causing variants reside, reducing data-generation and storage requirements relative to WGS; while still providing extensive clinically relevant genomic coverage. Because WES targets all protein-coding regions and WGS interrogates essentially the entire genome, both approaches generate comprehensive datasets from which 'virtual' gene panels can be constructed. As clinical evidence evolves, the ECS panel content can be modified *in silico* without altering the wet-lab workflow, enabling rapid incorporation of newly validated disease genes or variants. In addition, retained sequence data allow retrospective reanalysis to assess additional genes or variant types not included in the initial analysis, which is not possible with fixed TGP designs. WES targets the protein-coding regions of the genome and flanking intronic sequences, using capture or amplification techniques to enrich these loci prior to sequencing. Since coverage across the exome can be uneven, certain regions may have insufficient depth or quality, potentially lowering analytical sensitivity relative to targeted panels; as a result, supplemental assays are often required to fill coverage gaps or assess difficult regions. In contrast, WGS does not rely on enrichment steps and therefore generates more uniform coverage across the genome. This enables simultaneous detection of SNVs, CNVs, repeat expansions, and other variant classes. However, typical WGS workflows produce lower read depth than WES or TGPs, which may reduce sensitivity for some variants.

2. Orthogonal/ supplementary methods

Laboratories should recognise when the DNA sequence characteristics of specific genes complicate variant detection or interpretation and determine when supplementary methods are needed to ensure adequate coverage of clinically relevant variant types. Certain genes contain pseudogenes, recurrent inversions, segmental duplications, or other architectures that limit standard short-read HTS performance. Laboratories should predefine orthogonal workflows, used either as primary assays for difficult loci or as confirmation of HTS findings in order to ensure high sensitivity for such variants.

Common examples of technically challenging gene analysis include: *CYP21A2* gene, where high homology to *CYP21A1P* and complex gene rearrangements necessitates locus-specific long-range PCR with downstream HTS or Sanger sequencing; *F8* intron-22 and intron-1 inversions, best detected with inverse (shifting) PCR or validated ddPCR assays; *SMN1/SMN2* copy-number assessment for SMA, for which MLPA remains a clinical reference method with qPCR or droplet digital PCR (ddPCR) as validated alternatives; and HBA1/HBA2 (α-globin) deletions/duplications, typically assayed by gap-PCR and/or MLPA. *FMR1* CGG repeat expansions, associated with fragile X-related disorders, are typically detected using triplet-primed PCR (TP-PCR), often in combination with capillary electrophoresis or Southern blot for sizing. Genes with closely related pseudogenes such as *GBA1/GBAP1* may also require long-range PCR or long-read sequencing to resolve recombinant alleles and complex rearrangements. Test menus should specify when orthogonal methods are reflexed, and validation reports should document assay limits and gene-specific blind spots.

Table 4. Overview of laboratory methods used in ECS, including detectable variant types, representative genes, and technical considerations.

Method	*Variant Classes*	*Gene Examples*	*Notes*
HTS (hybrid-capture or amplicon)	SNVs, small indels; some CNVs	*CFTR, PAH, GALT*	Primary platform for most ECS panels
HTS CNV callers	Multi-exon deletions/duplications	*GJB2, STRC, DMD*	Performance depends on gene coverage, uniformity; validation required
MLPA	Exon-level CNVs, gene conversions	*SMN1, HBA1/HBA2, DMD*	Gold standard for SMA and α-thalassemia
qPCR	Gene-level copy number	*SMN1, CYP21A2*	High precision; suited for silent-carrier detection
Inverse PCR/ddPCR	Recurrent inversions and complex rearrangements	*F8*	Detects F8 intron-22 and intron-1 inversions not reliably identified by short-read HTS; widely used in haemophilia A testing
Triple-primed PCR	Repeat expansions	*FMR1, FXN*	Needed for sizing large repeats
Long-range PCR	Pseudogene resolution, gene conversions	*GBA/GBAP, CYP21A2/21A1P, SMN1/SMN2*	Resolves high homology regions; often followed by Sanger sequencing or short read HTS.
Long-read sequencing	Repeat expansions, homology, structural variants	*FMR1, FXN, GBA*	Emerging clinical adoption

Technical Considerations for Variant Detection and Bioinformatics considerations

Accurate variant detection in ECS requires validated bioinformatic pipelines for sequencing data alignment, variant calling, annotation, and CNV inference. Analytical performance, including sensitivity and specificity, must be well established for all relevant variant classes including SNVs, small indels, CNVs, and other variants in complex genomic loci as these

parameters differ across methods and genes. DNA regions with pseudogenes, segmental duplications, or extreme GC content warrant particular scrutiny due to increased false-positive and false-negative rates.

Many clinical laboratories rely on third-party or external bioinformatic pipelines for core NGS processing steps, including read alignment, variant calling, and annotation. When using these tools, it is essential that their performance characteristics are well understood, appropriately validated, and periodically re-evaluated; particularly after major software, algorithm, or database updates. Alignment should be performed against a validated reference genome build (GRCh37 or GRCh38), and the reference assembly, annotation tools, and downstream analysis pipeline must all use the same build to avoid coordinate or annotation discrepancies. Consistent transcript selection is also critical for accurate variant interpretation, as many genes have multiple transcripts with alternative exons and differing clinical relevance. Standardised transcript sets such as MANE Select and MANE Plus Clinical help ensure uniform interpretation across laboratories and allow variant annotations to remain compatible with widely used resources, including ClinVar and other curated variant databases.

Exon-level CNVs represent an important pathogenic mechanism in several ECS-relevant genes, including SMN1, DMD, GJB2, and HBA1/HBA2. HTS based CNV callers can identify many of these variants, however their performance varies across sequencing platforms and bioinformatic pipelines. Their sensitivity is influenced by read depth, coverage uniformity, GC content, and the size of the event. Robust validation studies are therefore required to characterise CNV-calling performance, define analytical thresholds, and establish assay limitations. When sensitivity for specific CNV classes is insufficient, confirmation with orthogonal methods may be necessary.

Recommendations

ECS may be performed using TGPs, WES, or WGS. The selected approach should be justified based on clinical scope, laboratory resources, and the anticipated need for future panel expansion or variant reinterpretation
Laboratories should validate and document analytical sensitivity and specificity for single-nucleotide variants (SNVs), small insertions/deletions (indels), copy-number variants (CNVs), and other structural variants, and reassess performance following any significant changes to assay chemistry, bioinformatics pipelines, or instrumentation.
Gene-level coverage metrics and technically challenging genomic regions (e.g., pseudogenes, regions of high sequence homology, repetitive elements, or extreme GC content) should be systematically evaluated. Known technical limitations affecting variant detection must be clearly documented and reported.
When HTS-based detection is unreliable or insufficient, particularly for CNVs or technically challenging regions, orthogonal methods (e.g., Sanger sequencing, MLPA, qPCR, or long-range PCR) should be employed to supplement or confirm variant detection, as appropriate.

Quality assurance and standards

The implementation of ECS requires stringent quality management (QM) and accreditation of the genetic laboratory to ensure accuracy of the testing process and reliable results. High-quality laboratory practices and validated interpretation of results are critical to provide high and consistent quality service to the patients and have a direct impact on their reproductive choices (Moyer et al., 2025).

Effective QM for ECS involves four key elements: planning, control, assurance, and improvement (Moyer et al., 2025). Quality planning requires standard operating procedures (SOPs) covering all testing stages, from panel design, to sample collection, data analysis and reporting. Quality control (QC) includes internal controls, risk assessments, proficiency tests, and regular equipment and reagent validation. Quality assurance is achieved through participation in internal and external quality assessment (IQA/EQA) programs, enabling laboratories to benchmark performance. Several EQA schemes exist for both the technical aspects of HTS-based testing and variant interpretation, including the recent GenQA pilot scheme for reproductive ECS, which provides an external proficiency framework for providers (https://genqa.org/eqas/RPCS). Quality improvement uses insights from these activities to optimize laboratory processes. In addition to the four traditional pillars of quality management, the procedure specifically for an HTS based laboratory testing, requires robust bioinformatics pipeline and secured data storage, due to the large volumes of genetic data generated through processing.

Accreditation by recognised professional bodies is a key indicator that laboratories meet high standards of quality and is closely linked to effective QM. Laboratories should pursue accreditation from organisations such as the College of American Pathologists (CAP; https://www.cap.org/) or the International Organization for Standardization (ISO 15189; https://www.iso.org/standards.html), which provide guidelines on laboratory quality and competency. Thorough documentation of all processes, QC measures, proficiency testing results, and consistent reporting is essential for clinical reliability. Finally, accreditation requires a commitment to continual improvement, with regular process review and optimization informed by proficiency testing, audit feedback, and scientific advances.

Achieving high specificity is critical in ECS to prevent false-positive carrier designations, which can lead to unnecessary anxiety and additional testing. Specificity is ensured through high-fidelity sequencing or genotyping protocols with stringent quality thresholds, the use of well-curated variant interpretation frameworks, and confirmation of reportable variants with orthogonal methods, particularly for technically challenging regions. Ongoing proficiency testing, inter-laboratory comparisons, and adherence to guidelines such as those from the ACMG on variant curation and technical considerations further support assay accuracy and reliable clinical reporting (Rivera-Muñoz et al., 2018).

Overall, the quality of all genetic testing is highly dependent on current scientific knowledge and technological competence. Effective QM, coupled with accreditation and adherence to

best-practice standards, is therefore essential to ensure that ECS is reliable, accurate, and, most importantly, clinically meaningful.

Recommendations

Participation in EQA schemes is recommended.
Laboratories should pursue accreditation from organisations which provide guidelines on laboratory quality and competency.
Adherence to relevant national and international best-practice guidelines is recommended.

Conclusion

These ESHRE Good Practice Recommendations on ECS serve as a comprehensive guide to practitioners currently offering or considering offering ECS to patients. The recommendations in this Good Practice Recommendations paper are supported by data from the literature, if available, and the expertise of the working group. These recommendations are intended to complement previously published guidance documents (ACOG, 2017a, Capalbo et al., 2022, Edwards et al., 2015, Vendrell et al., 2025). This ESHRE Good Practice Recommendations paper provides recommendations on core principles for eligibility, timing, panel design, result interpretation, counselling, and ethical governance. Central to these recommendations is the recognition that ECS is a screening tool aimed at identifying reproductive risk, rather than a diagnostic test, and that its primary objective is to support reproductive autonomy through informed choice.

Table 5 Summary of ESHRE's recommendations for the application of ECS in MAR

Population	Timing	Conditions	Reporting	Consent	Counselling	Partner Testing	Quality & Notes
MAR PATIENTS, GAMETE DONORS	Preconception preferred to ensure all reproductive options are available	Prioritize inclusion of serious, early-onset, and clinically well-defined AR and XLR disorders with clear genotype-phenotype correlations. Conditions tested in newborn screening should be included when they provide reproductive benefit.	Only clinically significant variants reported (P/LP). Two ECS reporting models can be considered: 1. Individual reporting 2. Combined reporting assessing the reproductive risk (couple report in autologous cycles or genetic matching report in gamete donation cycles).	Pre-test information mandatory with sufficient time to decide. Consent must ensure informed and voluntary participation.	Generic pre-test information for all; post-test counselling mandatory for carrier couples. Counselling to include discussion on residual risk, test limitations and implications for relatives	Simultaneous testing is preferred for immediate risk assessment and to avoid delays.	Participation in EQA schemes Laboratory accreditation Adherence to guidelines/ recommendations

Future areas for research

Emerging challenges and opportunities in ECS

ECS remains important in the current healthcare landscape, which is only able to treat a limited number of the thousands of known genetic diseases. While the number of conditions being successfully managed with novel orphan drugs and emerging technologies, including gene therapies, is steadily increasing, this progress remains slow, costly, and constrained by stringent regulatory frameworks — limiting their integration into mainstream healthcare for

the vast majority of affected individuals (Boycott et al., 2013, Tambuyzer et al., 2020). At the same time, ongoing advances in genetic research are expected to generate new evidence on gene-disease associations and variant interpretation, supporting the continuous refinement and expansion of ECS panels (Strande et al., 2017). As a result, preconception and prenatal carrier screening remain, to date, the most effective strategy for preventing the birth of severely affected children, and ECS continues to be a vital tool for identifying genetic risks in reproductive medicine (Henneman et al., 2016, Kirk et al., 2024).

Looking ahead, technological advances are revealing an expanding landscape of non-coding genes with recessive inheritance underlying severe childhood conditions. To date, only a handful of such genes have been firmly linked to severe disease — most notably small nuclear RNAs involved in splicing, such as RNU4-2, RNU2-2, and RNU4ATAC — which typically cause profound neurodevelopmental or multisystem disorders (Baillat & Bhatt, 2024; Emmett et al., 2024; Holling et al., 2024). However, this small number reflects historical limitations rather than true biological rarity: clinical sequencing has historically focused on protein-coding regions, leaving non-coding genes largely underexplored (Encode Project Consortium, 2012, Mattick et al., 2023). As large population studies begin to characterise the carrier frequency and disease burden associated with these loci, ECS panels may need to expand to include them — applying the same rationale underpinning current screening: if a gene contributes significantly to severe, early-onset disease and carriers are not extremely rare, identifying at-risk couples carries clear clinical value (Gregg et al., 2021, Sagaser et al., 2023).

Incorporating non-coding genes into ECS will not be straightforward, however. It will likely require broader adoption of WGS over exome-based approaches, alongside improved frameworks for non-coding variant interpretation — since many clinically relevant variants lie outside coding regions, are harder to assess functionally, and are frequently missed or filtered out by current bioinformatics pipelines (Jaganathan et al., 2019, Rentzsch et al., 2021, Smedley et al., 2021). In summary, while we are at an early stage — with few genes identified so far — the potential for expansion is substantial, and could meaningfully reshape future carrier screening as both genomic evidence and sequencing technologies continue to evolve (Boycott et al., 2013, Gilissen et al., 2014).

Expanding the scope of preconception genomics

As ECS increasingly relies on high-throughput sequencing technologies, the potential identification of secondary findings represents an important area for future research. Clear frameworks are needed to define which findings, if any, should be actively sought or reported beyond the primary reproductive scope of ECS. This includes evaluating the clinical relevance, actionability, and ethical implications of reporting medically actionable variants unrelated to reproductive risk, while ensuring that ECS remains primarily focused on reproductive decision-making.

Secondary findings

An area of emerging interest concerns the broader health implications of infertility itself. Epidemiological studies increasingly suggest that both male and female infertility may represent an early marker of increased risk for certain chronic conditions later in life. Preliminary evidence has suggested that individuals presenting with infertility may carry a higher burden of pathogenic variants in genes included in medically actionable gene lists, such as those proposed by the ACMG (Lee et al., 2025b).In this context, the preconception period may provide a unique opportunity to identify individuals with an increased genetic risk profile at an earlier stage of life, potentially enabling timely preventive strategies.

However, the potential expansion of ECS to include genetic risk factors for non-reproductive conditions requires careful evaluation. Current ECS assays are primarily designed and validated for carrier screening genes and are not analytically optimised for diagnostic testing of genes associated with medically actionable adult-onset disorders. Expanding the scope of ECS to include such genes would therefore require substantial analytical adaptations, rigorous preclinical validation, and careful consideration of ethical, counselling, and health-system implications. Further research is needed to assess the clinical validity, utility, and psychosocial impact of incorporating broader genomic risk information into preconception screening programs.

Infertility, embryonic lethality, and recessive causes of pregnancy loss

Future research should explore the potential inclusion of genes associated with infertility phenotypes and adverse reproductive outcomes within ECS frameworks. Emerging evidence suggests that pathogenic variants linked to embryonic or fetal lethality may contribute to unexplained reproductive failure, including implantation failure and miscarriage (Arnadottir et al., 2025). In addition, recessive monogenic conditions leading to such outcomes may represent another relevant category. Recent studies indicate that a proportion of pregnancy losses in chromosomally normal foetuses may be attributable to inherited monogenic disorders, which in principle could be anticipated through preconception ECS. Integration with established infertility-related genetic testing may contribute to earlier identification of underlying causes of reproductive failure, more personalised clinical management, and improved reproductive planning.

However, the current evidence base supporting many candidate genes remains limited. Uncertain penetrance, variable expressivity, and incomplete genotype phenotype correlations may increase the likelihood of ambiguous findings and complicate counselling. Furthermore, many studies describing genes associated with oocyte maturation defects or embryonic developmental arrest have been conducted in specific ancestral populations or consanguineous families, limiting the generalisability of these associations to broader populations. Prospective studies will therefore be required to validate these genetic associations, define clinically meaningful predictive values, and establish evidence-based frameworks for counselling and informed reproductive decision-making.

Despite these limitations, expanding preconception genomic testing to include carefully curated infertility related and embryonic lethal genes represents a promising area of research. If appropriately validated, such approaches may increase the diagnostic yield of genome-based testing in preconception screening and improve understanding of the genetic architecture underlying reproductive failure.

Implementation challenges, equity, and governance of ECS programs

Future research should also focus on the practical implementation of ECS within diverse healthcare systems. Despite growing interest, integrating ECS into existing reproductive care pathways, including MAR programs, remains challenging. Key barriers include limited availability of trained genetic counsellors or clinical geneticists, the need for validated alternative delivery models (e.g., digital or mainstreamed), differences in laboratory capacity and accreditation standards, and variability in reimbursement policies across healthcare systems. Research is therefore needed to identify scalable models for delivering ECS, including innovative counselling approaches, digital decision-support tools, and multidisciplinary care pathways.

Ensuring equitable access represents another important priority, as differences in funding models, availability of genetic services, and national regulatory frameworks may lead to disparities in access across healthcare systems, particularly in the context of cross-border reproductive care. In parallel, the ethical framework governing ECS implementation requires ongoing attention. A longstanding tension exists between the autonomy paradigm — which prioritises informed reproductive choice — and the preventive aim of reducing the incidence of severe genetic conditions, with the additional obligation of considering the welfare of the future child. The prevailing consensus holds that ECS should be offered as a voluntary, non-directive screening option, empowering individuals and couples without exerting moral pressure — a concern particularly relevant in MAR, where patients may be especially vulnerable to the commercialisation or "upselling" of genetic tests. At the same time, a more directive approach may be ethically justified for couples identified as being at high risk for a serious AR condition, where considerations of the future child's wellbeing may appropriately inform clinical guidance. In the context of gamete donation, these ethical considerations are further amplified, as single donors are frequently used across multiple families, increasing the potential population-level impact of undetected carrier status. Harmonising ethical standards across jurisdictions — including criteria for donor screening, management of incidental findings, matching test policies, and protocols for at-risk couples — remains an unresolved challenge that future research and policy work should prioritise.

At the same time, the increasing use of genomic sequencing technologies in ECS raises important considerations regarding data governance, privacy, and long-term management of genomic data. Future studies should support the development of harmonised frameworks for secure data storage, responsible sharing of variant information, and appropriate mechanisms for variant reinterpretation and patient recontact as knowledge evolves. Finally, systematic

evaluation of real-world outcomes will be essential to assess the clinical utility of ECS programs. Embedding standardised outcome metrics, longitudinal follow-up, and registry-based evaluation will help clarify the impact of ECS on reproductive decision-making, psychosocial wellbeing, and clinical outcomes such as time to pregnancy and use of reproductive options.

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Supplementary information

- S1: List of abbreviations
- S2: List of recommendations
- S3: Recommendations for future research
- S4: List of participants to the stakeholder review

Supplementary Data S1 – List of abbreviations

Abbreviation	Explanation
ACMG	American College of Medical genetics and genomics
ACOG	American College of Obstetricians and Gynaecologists
AR	Autosomal Recessive
ARC/ARCs	At-Risk Couple(s)
B	Benign
CAP	College of American Pathologists
CCMG	Canadian College of Medical Geneticists
CF	Cystic Fibrosis
CLIA	Clinical Laboratory Improvement Amendments
CNV	Copy Number Variant
CR	Carrier Rate
ECS	Expanded Carrier Screening
ESHG	European Society of Human Genetics
ESHRE	European Society of Human Reproduction and Embryology
FDR	Fetal Disease Risk
FMR1	Fragile X Messenger Ribonucleoprotein 1
FSH	Follicle-Stimulating Hormone
FXS	Fragile X Syndrome
GCF	Gene Carrier Frequency
GCS	Genetic Carrier Screening
GDR	Gene-disease relationship
GPR	Good Practice Recommendation
HGSA	Human Genetics Society of Australasia
HTS	High-Throughput Sequencing
IANZ	International Accreditation New Zealand
IF/IFs	Incidental Finding(s)
ISO	International Organisation for Standardisation
IVF	*In vitro* Fertilisation
JSHG	Japan Society of Human Genetics
LB	Likely Benign
LLM	Large Language Model
LP	Likely Pathogenic
MAR	Medically Assisted Reproduction
MLPA	Multiplex Ligation-dependent Probe Amplification
NATA	National Association of Testing Authorities

NGS	Next Generation Sequencing
NIPT	Non-invasive prenatal testing
NSGC	National Society of Genetic Counsellors
P	Pathogenic
PGT-M	Preimplantation Genetic Testing for Monogenic Disease
PND	Prenatal Diagnosis
POI	Primary Ovarian Insufficiency
QC	Quality Control
QM	Quality Management
SF/SFs	Secondary Finding(s)
SIG	Special Interest Group
SMA	Spinal Muscular Atrophy
SMN1	Survival Motor Neuron 1
SNV	Single-Nucleotide Variant
SOP	Standard Operating Procedure
TGP	Targeted Gene Panel
TSD	Tay-Sachs Disease
VCF	Variant carrier frequencies
VUS	Variants of uncertain significance
WES	Whole Exome Sequencing
WG	Working group
WGS	Whole Genome Sequencing
XLR	X-Linked Recessive

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Supplementary Data S2 - List of recommendations

	Recommendations
1.	**Clinical implementation**
1.1	All individuals undergoing MAR, including gamete donors, are eligible for ECS.
	The preconception period is the preferred timing for ECS in MAR to maximise clinical and reproductive benefit.
	It is recommended to do simultaneous testing of both partners.
1.2	ECS panels developed through transparent, evidence-based processes aligned with professional society guidelines should be selected.
	Serious, early-onset, and clinically well-defined AR and XLR disorders with clear genotype-phenotype correlations should be prioritised.
	Panel inclusion should not be restricted to conditions currently eligible for PGT-M or listed in national pre-approved gene lists, provided they meet established clinical validity and severity criteria.
	Conditions included in newborn screening programs should be considered for inclusion when they provide clear reproductive benefit.
	Gene panels should undergo periodic re-evaluation to incorporate newly validated gene–disease associations, improved variant annotation, and refined severity frameworks.
	Clear documentation should be available on the methodologies used to define gene-panel content, and reporting policies.
	ECS test should be analytically validated, performed in an accredited laboratory, and accompanied by clear and clinically interpretable reports.
	Reporting should be limited to pathogenic and likely pathogenic variants.
1.3	Two ECS reporting models can be considered: 1. Individual reporting: each individual receives their own ECS report, with results interpreted in the context of the specific couple. 2. Combined reporting: a combined report assessing the reproductive risk is provided (couple report in autologous cycles or genetic matching report in gamete donation cycles).
	The choice of reporting strategy should be guided by available resources and local regulations during genetic counselling.
	Individuals should retain the right to access their personal genetic information, regardless of the reporting model used.
	All tested individuals, including donors, should have the opportunity to opt in or opt out of receiving individual-level results.
	ECS may reveal incidental findings; this must be disclosed in the consent and individuals should have the option to opt out of receiving such findings.
	Interpretation of ECS results should be seen in a binary high vs low risk fashion.
	When panels differ between partners/donor–recipient, an alternative is performing reflex testing (“match testing”), in which ECS is first performed in one partner, and the counterpart is subsequently tested only for the genes or variants identified.
2.	**Genetic counselling and informed consent**

2.1	Genetic counselling is essential for all individuals/couples considering ECS due to the test's screening nature, implications, and limitations.
	Pre-test genetic counselling should be provided to support autonomous, informed reproductive decision-making.
	Pre-test genetic counselling should provide clear education on the optional nature, scope, limitations, residual risk, possible incidental findings, and potential reproductive implications of ECS to support fully informed, autonomous decision-making before testing.
	Informed consent should be obtained prior to ECS and should explicitly document that individuals/couples have been informed about the scope, limitations and implications of testing.
2.2	Post-test counselling should be mandatory for the at-risk couples and individuals with a positive result.
	Post-test counselling should be recommended for couples at low risk. Other pathways are acceptable, given that these are validated.
	Post-test genetic counselling should deliver result-specific guidance tailored to the level of risk, and including clinical implications, residual risk, emotional impact, family communication, and reproductive options.
	Referral to appropriate specialist care should be ensured in cases of high-risk results or clinically significant incidental findings.
	Genetic counselling may be performed either individually or in the presence of both members of the couple, depending on the nature of the result; couple-based counselling is particularly recommended for high-risk results, whereas individual counselling may be acceptable for low-risk results.
2.3	Informed consent should reflect full understanding of ECS's purpose, nature, benefits, limitations, and implications for the individual and family.
	Donors should be able to receive their results; the consent form should also mention that donors can opt out of receiving their results.
2.4	It is recommended not to reject donors only based on their carrier status for an AR disease.
	The recipient should be notified of reproductive options.
	Constant monitoring and review of ACRs rates and reproductive decision outcomes is recommended to inform and improve ECS practice over time.
3.	**Ethical issues**
	In MAR, ECS should be offered as a voluntary, non-directive screening test to patients without known genetic risks, and individuals should not be pressured to undergo testing or to act upon results.
	Couple identified as carriers for a serious AR condition are expected to consider preventive reproductive options if they wish to conceive through MAR.
	In gamete donation, if the carrier status of the donor is available, three options are available: recipients could be a) informed of the donor's carrier status, b) only informed of the most frequent and severe pathogenic variant identified, or c) not informed about donor carrier status at all.

	If the recipients are made aware of the positive carrier status of their donor for a severe condition, they should be offered a ECS or match test, or the possibility to change donor, while receiving adequate counselling.
	If the recipients refuse to take a match test or change donor, they should sign a waiver document. The patients' choice should be respected and not affect the care proposed.
4.	**Technical consideration, technological approaches and future directions.**
4.1-4.5	ECS panel design should follow a structured, transparent, and evidence-based process.
	Laboratories may adopt either a clinical-first or data-driven approach, depending on clinical context and available resources.
	Panels should prioritise severe and profound childhood-onset conditions; moderate conditions may be included where they have a meaningful impact on reproductive decision-making.
	Mild, low-penetrance, or adult-onset conditions should not be included.
	Only genes with well-established gene–disease relationships should be included, based on structured evaluation frameworks. Genes with limited or conflicting evidence should not be included.
	ECS should be implemented as a pan-ethnic screening approach. Differences in carrier frequency across populations should be considered, and population-specific adaptations may be applied where justified.
	Gene carrier frequency estimates should be derived from datasets with adequate sample size, appropriate population representation, and robust methodological quality. Where feasible, multiple independent data sources should be used.
	Laboratories should meet established best-practice standards, including use of validated public variant databases, explicit acknowledgment of gene-specific technical limitations, and the application of confirmatory methods where appropriate.
	ECS panels should be regularly reviewed and updated, with transparent processes for the addition or removal of conditions.
4.6-4.7	ECS may be performed using TGPs, WES, or WGS. The selected approach should be justified based on clinical scope, laboratory resources, and the anticipated need for future panel expansion or variant reinterpretation
	Laboratories should validate and document analytical sensitivity and specificity for single-nucleotide variants (SNVs), small insertions/deletions (indels), copy-number variants (CNVs), and other structural variants, and reassess performance following any significant changes to assay chemistry, bioinformatics pipelines, or instrumentation.
	Gene-level coverage metrics and technically challenging genomic regions (e.g., pseudogenes, regions of high sequence homology, repetitive elements, or extreme GC content) should be systematically evaluated. Known technical limitations affecting variant detection must be clearly documented and reported.
	When HTS-based detection is unreliable or insufficient, particularly for CNVs or technically challenging regions, orthogonal methods (e.g., Sanger sequencing, MLPA, qPCR, or long-range PCR) should be employed to supplement or confirm variant detection, as appropriate.
4.8	Participation in EQA schemes is recommended.

	Laboratories should pursue accreditation from organisations which provide guidelines on laboratory quality and competency.
	Adherence to relevant national and international best-practice guidelines is recommended.

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Supplementary Data S3 - Recommendations for future research

Longitudinal studies should be conducted to re-evaluate the clinical validity of ECS panel genes as population-level genomic databases expand and diversify, and to assess emerging gene-disease associations — including non-coding genes — to inform the periodic refinement and evidence-based expansion of carrier screening panels and related analytic technologies.

Research should evaluate the clinical validity, utility, psychosocial impact, and health-system implications of expanding ECS to include genetic risk factors for non-reproductive, adult-onset conditions.

Future research should explore the inclusion of genes associated with infertility phenotypes, embryonic lethality, and recessive causes of pregnancy loss within ECS frameworks, with rigorous validation of genotype-phenotype correlations across diverse populations.

Research should identify and validate scalable, equitable models for ECS delivery across diverse healthcare systems, including digital counselling tools, mainstreamed care pathways, and multidisciplinary approaches adaptable to varying resource settings.

Standardised outcome metrics and registry-based evaluation tools should be developed to enable systematic assessment of the real-world impact of ECS on reproductive decision-making, psychosocial wellbeing, and clinical outcomes.

Supplementary Data S4 - List of participants to the stakeholder review

Reviewer	Country	Participation on behalf of (if any)