2020

ESHRE Ethics committee

The Ethics of Preconception Expanded Carrier Screening in Applicants of Assisted Reproduction

GPR paper of the European Society of Human Reproduction and Embryology

REVIEW REPORT

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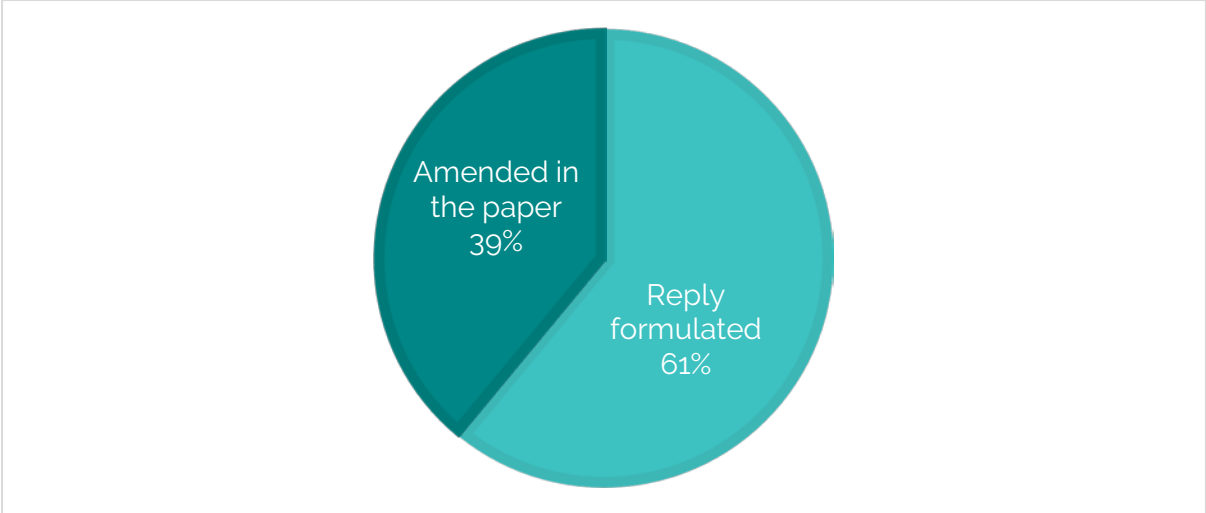
The draft of the paper "The Ethics of Preconception Expanded Carrier Screening in Applicants of Assisted Reproduction" was published for public review for 6 weeks, between 4 July and 17 August 2020.

This report summarizes all reviewers, their comments and the reply of the writing group and is published on the ESHRE website as supporting documentation to the paper.

During the stakeholder review, a total of 46 unique comments were received from 8 reviewers, including 2 representatives of professional organisations.

The comments were focussed on the content of the guideline (41 comments), language and style (3 comments), or were positive remarks that did not require a reply (2 comments). All suggested language corrections were adapted.

All comments to the content of the paper (n=41) were checked by the writing group and the Ethics Committee and either addressed (in the paper) or a reply was formulated. Of the 41 comments, 16 (39,0%) resulted in an adaptation to the text, while 25 (60.9%) were replied to in this report.



Experts that participated in the stakeholder review

The list of representatives of professional organization, and of individual experts that provided comments to the guideline are summarized below.

Representatives of professional organisations

Organisation	Country	Representative
Public and Professional Committee of the European Society of Human Genetics (ESHG)	UK	Francesca Forzano
Italian society of human reproduction	Italy	Francesca Spinella

Individual experts

Reviewer	Country
Anne-Bine Skytte	Denmark
Marja Visser	The Netherlands
Carlos Calhaz Jorge	Portugal
Mário Sousa	Portugal
Thomas Tapmeier	Australia
Valerie Shaikly - Karen Sage	UK

Reviewer comments and replies

Name	Page	Line	Comment	Reply
Anne-Bine Skytte	2	77	"applicants of MAR using their own gametes" Almost all MAR applicants are using their own gametes, very few use double donation, hence the definition is challenging	"applicants of MAR using their own gametes" is mentioned to clarify that the scope of the papers is for couples using their own gametes, not for couples using donor gametes,
Anne-Bine Skytte	2	50	If donor gametes are a condition in the primary counselling, one need to know if they should undergo the same ECS screening (Same comment for page 4, line 152; page 5, line 182; page 11, line 393)	Gamete donor screening is beyond the scope of the current manuscript. Donor gametes are only discussed as a reproductive option for carrier couples.
Anne-Bine Skytte	6	221-239	How do we enable autonomous reproductive choice for single women and same sex couples using this guideline?	Reproduction in same-sex couples would require the use of donor gametes, which is beyond the scope of this manuscript (cf. Abstract and Introduction).
Anne-Bine Skytte	8	295	Does this also apply to single women and same sex couples?	Reproduction in same-sex couples would require the use of donor gametes, which is beyond the scope of this manuscript.
Anne-Bine Skytte	16	634 - 637	Some of the issues mentioned, are they not applicable to X-linked disorders too, pre-mutations, and skewed X-inactivation? Where penetrance is hard to predict? Is the restriction to AR and X-linked? Or just AR?	The Committee is hesitant to delete X-linked disorders. Possible specifics of ECS for X-linked disorders may be found and reflected upon in the envisaged pilots.
Anne-Bine Skytte	17	666	What about the equity between heterosexuals vs single moms and same sex couples?	Reproduction in same-sex couples and single moms would require the use of donor gametes, which is beyond the scope of this manuscript (cf. Abstract and Introduction). Therefore, further aspects of same-sex couples and single moms are not discussed
Anne-Bine Skytte	20	781	An ethical objection could be discrimination if it is only offered to heterosexual couples?	Reproduction in same-sex couples and single moms would require the use of donor gametes, which is beyond the scope of this manuscript (cf Abstract and Introduction). Therefore, further aspects of same-sex couples and single moms are not discussed

Marja Visser	2	50	This is a carefully written and worthful document. The only serious comment I have about the 'or using donor gametes". This is really a different type of pro-creation ans should not be mentioned in this paper, or make a serious paragraph about the difference etc. In case a couple does not meet the reasonable welfare standard, you should better do nothing. (Same comment for page 7, line 271; page 8, line 2960; page 9, line 320; page 21, line 799)	When mentioning donor gamete use, we aim to tick off different preventive options for carrier couples: the use of donor gametes is one of the options. To disregard this in the counselling and in this text would be problematic, while elaborating on this option in this manuscript would be beyond its scope.
Carlos Calhaz Jorge	General comment - 1		Many thanks to the authors for this paper on an extremely complex and sensitive topic.	Thank you
Carlos Calhaz Jorge	General comment - 2		There is a tendency to replace the "old" ART by the "modern" MAR. But they have different meanings and are not interchangeable. According with the last International glossary, 2017: *Medically assisted reproduction (MAR): Reproduction brought about through various interventions, procedures, surgeries and technologies to treat different forms of fertility impairment and infertility. These include ovulation induction, ovarian stimulation, ovulation triggering, all ART procedures, uterine transplantation and intra-uterine, intracervical and intravaginal insemination with semen of husband/partner or donor.* *Assisted reproductive technology (ART): All interventions that include the in vitro handling of both human oocytes and sperm or of embryos for the purpose of reproduction. This includes, but is not limited to, IVF and embryo transfer ET, intracytoplasmic sperm injection ICSI, embryo biopsy, preimplantation genetic testing PGT, assisted hatching, gamete intrafallopian …* In short, MAR includes ART plus surgery and ovulation induction and IUI and uterine transplantation and so on! So, I guess all the text refers to ART candidates/applicants not MAR candidates.	The manuscript indeed focuses on the offer of ECS to patients applying for IVF or IVF/PGT, who are already aware of the burdens involved with treatment and may therefore be particularly interested in ECS (line 82 & 163 etc.). But clearly, the broader group of prospective parents applying for other types of MAR (linked with in vivo conception) may be interested in ECS for similar reasons. The Cie. prefers to stick to the current focus on ART-patients and make use of the widely accepted term assisted reproduction.
Carlos Calhaz Jorge	General comment - 3		ECS is at the moment accessible to only a small proportion of clinics in some countries. And in many of them only to couples that can afford it. Would the authors elaborate more on the ethics conflicts concerning injustice in inequity of access to ECS based in financial individual possibilities?	The authors agree with this comment, and added a sentence on this topic in the section on justice.
Carlos Calhaz Jorge	General comment - 4		Just a single sentence refers to the risk of commercialization in this matter (line 678). And the risk is huge! Maybe the authors could give some more attention to that specific topic.	A sentence was added stating "Patient interest, not commercial interest, should determine clinical care."
Carlos Calhaz Jorge	2	48-50	I consider too definitive to state that "it is good practice to give carrier couples of serious disorders … access to ART only on the condition that they apply for PGT-M…". Couples may decide to go for prenatal diagnosis instead. And more if practical local conditions (costs, accessibility,…) precludes easy access to PGT. (Also line 797-800)	We amended the text accordingly, specifying the option of prenatal diagnosis. We also the modified sub-section on Professional Responsibilities, pp.7-8.

Carlos Calhaz Jorge	4	162	"In European countries 2 to 6 percent of births are achieved by means of MAR". In fact those numbers refer to ART. No data exist concerning surgeries, ovulation induction or ovarian stimulation (outside ART) to allow to express contribution of MAR to the countries natality	This was corrected in the text
Carlos Calhaz Jorge	8	Figure 1 and page 8	The relevance given to scenario (b) seems disproportionate to reality. To refuse ART application to a couple that decides not to be involved in ECS is unacceptable. I understand that later on the authors express this opinion but even as an intellectually driven exercise it is too much relevance in my opinion.	Scenario b cannot be disregarded/deleted, also taking account of the crucially important difference between b1 and b2. However we amended this Figure and the linked commentary in line with other comments and the revised Abstract.
Carlos Calhaz Jorge	12	445 - 446	References "Pereira et al, and Sosnay et al" are not included in the list of references of pages 23-26	This language error has been corrected. Thank you.
Mário Sousa	general		Portugal screens all newborn for congenital hypothyroidism and metabolic hereditary diseases (24 situations). In Portugal PGT is legally offered to infertile patients as PGT-A, TGT-SR and PGT-M according to the guidelines of ESHRE (ESHRE-HROpen 2020). Primary ciliary disease was not presented, and is also an important rare disease. As you mentioned, it is important to obtain information from geneticists and couples with affected children, and if in this document this was not performed, I think you should take that information.	The paper discussed whether the offer of expanded carrier screening to all ART couples is proportionate. Newborn screening is a different topic and outside the scope of the current paper, but a few lines were added on the topic.
Mário Sousa	14	547 - 552	After reading, as a clinician I would like to have in this manuscript the following Tables: -general criteria for seriousness (p 14, L547-552, with explanations for each)	As far as we know, there are no such tables - but there is some interesting literature (that we make use of in the next lines) about relevant criteria. Given the difficulties of making these criteria operational, we stress the importance of a procedural approach that takes account of the views of relevant stakeholders (line 554 etc.).
Mário Sousa	21	801 - 804	After reading, as a clinician I would like to have in this manuscript the following Tables: -main diseases ESHRE considers secure to be tested-with variant specified (P21, L801-804).	This would be a much to be welcomed outcome of the further research and reflection as recommended in the text.
Mário Sousa	general		I also would like to know the probability of getting an embryo devoid of pathologic variants.	This comment was discussed, but it was not entirely clear. We did add a sentence on expectation management and residual risk in the section on Informed consent and the art of counselling.
Thomas Tapmeier		0	'Proportionality' should be described as evolving, I think.	We consider this to be sufficiently clear from the text, also given its emphasis on research aimed at clarifying possible benefits and harms of ECS.

Thomas Tapmeier		291	'which' instead of 'what'	This language error has been corrected. Thank you.
Thomas Tapmeier		377	'fewer patients' instead of 'less patients'	This language error has been corrected. Thank you.
Thomas Tapmeier		549	A note on when NBS was introduced, and why. While the availability of NBS might not impede ECS, ECS in turn could negate the need for NBS. Perhaps a sentence on that?	The link between NBS and ECS is addressed below, in the Sub-section 'Smaller scope ECS?' We consider this sufficient.
Valerie Shaikly - Karen Sage	1	3	It may be valuable to consider amending the title referencing MAR-applicants using their 'own gametes'. This is not apparent until line13 and 23 of the abstract and emphasized on line 77 in italics. This omission could lead to inclusion of the paper in searches for guidance/ethics for patients using donor gametes. Our experience has shown that expanded carrier screening of donors is common place with variable interpretation by MAR staff. Appreciating such discussion is beyond the scope of the draft guidance, it would be beneficial to clarify the title (patients using donor gametes are also as applicants of medically assisted reproduction). A known donor or co-parent who provides gametes for treatment may also come under this guidance as a couple for the purposes of ECS. ECS often includes x-linked conditions so the principles would apply for a woman regardless of her partner status. Mention of these applicant categories would cover the spectrum of patients who present for MAR.	We prefer a shorter title for the document. Furthermore, we consider the current title to be sufficiently clear. The specification on the "own gametes" is mentioned in the first sentence of the abstract.
Valerie Shaikly - Karen Sage	2	47-50	Later links to conclusion on pages 20-21; lines 797-800). On offering preconception ECS in the general population. The following statement seems to removes the autonomy of informed reproductive choice. "Screening offer itself should be non-directive, it is good clinical practice to give carrier couples of serious disorders" .. .."access to MAR only on condition that they apply for PGTM or donor gametes" this seems coercive. It may be helpful to clarify here, that carrier couples in the general & sub-fertile population do have the option to conceive naturally or through MAR and still have prenatal choice. As well as other options of adoption/fostering/remain childless	This comment suggests that the principle of respect for autonomy is absolute – which is at odds with former documents of ESHRE stipulating the professional responsibility of doctors involved in assisted reproduction to consider the interests of children to be conceived. We have not amended the text based on this comment.
Valerie Shaikly - Karen Sage	2	50	Although alluded to later in the paper (line 151 and 208-222, 356)) the condition offering ECS if 'they apply for PGT-M or donor gametes' does not give MAR couples the autonomy to proceed without PGT-M testing or of not using of donor gametes. Some applicants may wish to continuing treatment and elect to have prenatal diagnosis with understanding of a 1 in 4 risk. This reproductive option is available to couples at risk who do not require MAR.	We amended the text accordingly, specifying the option of prenatal diagnosis. We also modified the sub-section on Professional Responsibilities, pp.7-8)
Valerie Shaikly - Karen Sage	3	81	Offering ECS to couples applying for MAR because of either 'subfertility or a high genetic risk of having an affected child.' It may be helpful to clarify that the high genetic risk that led them to seek MAR initially was independent of conditions included in ECS.	We think this suggestion is sufficiently clear in the text and decided not to clarify it.

Valerie Shaikly - Karen Sage	5	169	"the additional demands associated with ECS and PGD (following the identification of a shared genetic risk) would be lower for IVF patients than for other couples" (Cho et al., 2013). This is correct however the statement could be balanced by inclusion of reference to the information in line 732-747, the psychological impact of a co-carrier status in addition to fertility difficulties, also that PGT-M is likely to reduce the cumulative chances of treatment success to achieve a family as embryo numbers available for transfer are reduced. Many PGT-M laboratories also offer PGT-A as part of the reporting which is an additional test couples may not have anticipated and may not be a able to opt out of.	The Background Section only aims at illustrating the actual relevance of the topic 'ECS in assisted reproduction'. The concept is further discussed in the Section on Proportionality, and we added a reference to this section.
Valerie Shaikly - Karen Sage	7	249 - 253	Prospective parents, given their generally low a priori risk do not have a moral responsibility to take part in preconception ECS, but that proven carrier couples, given their high risk, may have a conditional moral responsibility to opt for avoidance, at least if the disorder is serious. "This also links later to (page 7; lines 267-268) – duty of MAR professionals to inform as posed by the question (page 7; lines270-272). May or should professionals recommend (in the interest of informed choice) ECS…. Our experience is that couples undergoing MAR are not informed of their a priori low risk of autosomal recessive carrier conditions, especially if their family history is unremarkable. So how do they know their risk? These couples are generally not counseled by their physicians, as evidence by the continued birth of CF and SMA babies after MAR in the UK, where the carrier frequency of the first condition (CF) is considered high enough in the general population to screen gamete donors but not a MAR couple, or even one partner of the MAR couple. It does seem inequitable to offer screening to gamete donors for a condition known to be prevalent in a population but then to NOT offer the same screening to couples? It may be helpful to clarify this point in this paper.	We tend to argue that this takes too far, as a detailed reflection on the (dis-)similarities between screening donors and screening applicants would require a separate paper. The issue of gamete donors is addressed elsewhere, the reference was added in the text.
Valerie Shaikly - Karen Sage	21	801	The conclusion could include an additional point: the need for a consensus for minimum requirements of the ECS in terms of clinical and analytical sensitivity and variants included. Our experience shows that detection rates can vary between ECS providers which then significantly impact residual risk. Our experience with applicants for ECS has demonstrated that there is the perception that the more genes included the better the test, which initiates a search for an ECS that is perceived as giving the best value.	A sentence as suggested was added to the conclusion.
Francesca Forzano	General comment - 1		The scope of the document is to discuss the ethics of preconception ECS for patients applying for medically assisted reproduction using their own gametes. Quite a few couples using egg or sperm donors would pay for those gametes and might choose to pay a priori an extra fee to screen the donor with ECS. Considering the costs implications, many are reluctant to choose	Reproduction requiring the use of donor gametes is beyond the scope of this manuscript (cf. Abstract and Introduction). As such gamete donor screening, selection and any costs associated with it are not discussed. We have clarified this in the text, including

		another donor. Would the document also cover these situations when mentioning couple's 'own gametes'?	a reference to an Ethical discussion of genetic screening of donors.
Francesca Forzano	General comment - 2	We agree that the screening offer itself should be non-directive and that it would be good clinical practice to offer reproductive options to couples identified as carrier of serious disorders. In the document, two scenarios are identified: the non-directive offer of testing and the offer as a precondition for access to MAR. This latter would be coupled with a coercive use of PGT-M or donor gametes. This latter scenario would seem more problematic from an ethical point of view. Moreover, considering that not all the couples would choose or would be eligible for PGT-M, or might refuse donor gametes, existing options such as NIPD or PD through CVS or amniocentesis are not taken into account. Can the authors explain why these routes have not been considered?	Based on another comment, we have added prenatal diagnosis as an option for carrier couples of serious disorders alongside PGT-M and donor gametes.
Francesca Forzano	General comment - 3	We would advise to replace the term "mutations" with "disease-causing variants" to align with international guidance on nomenclature.	We have adapted "mutations" to "disease-causing variant" as suggested by the reviewer.
Francesca Forzano	General comment - 4	The authors mention some differences between ECS for population screening and in the context of MAR. However, they do not discuss the reasons behind the lack of implementation of the ECS in the population at large which have still relevance in this specific context, and particularly the effectiveness of the ECS strategy (not demonstrated) and the quality of testing (often very poor). Albeit it is clearly stated that the focus of the document is an ethical reflection, and not a technical examination, it would be essential to take into account these two important requisites, even in a basic way, as these would impact the sensibleness of the offer of ECS per se and the counselling to the couples. Would ESHRE agree on a robust quality control for the companies offering the tests?	As stated by the reviewer, the paper provides an ethical reflection on ECS. ESHRE is considering a technical paper on the same topic, which would include the suggested considerations.
Francesca Forzano	General comment - 5	Choice of conditions to test in ECS. The discussion regarding the choice of disease to include revolves mainly around the severity of the conditions to be listed. As this is rightly discussed as difficult to classify, example criteria would be helpful. The frequency of disorders as criteria for positive selection is surprisingly not mentioned, although it should be one of the most important. Would ESHRE see themselves in the position to agree on/demand a minimal list of genes/diseases or on the other hand exclude groups of diseases (e.g. BRCA1/2) if ECS offer is direct to consumer? In some countries the list of diseases for which PGT can be offered is conditional to the approval of a dedicated institution, see for instance the role of HFEA in the UK. Would this list be matched to the ECS offer?	After discussion within the Ethics committee it was decided that a list of serious diseases for directing ECS was neither feasible nor preferable. The current paper aims to provide an ethical framework. Further operationalisation is to be performed in a multidisciplinary context and is outside the scope of the current project

Francesca Forzano	General comment - 6		The authors rightly mention that couple identified at risk of having a child affected with a recessive disorder might benefit of the offer of PGT-M. However, they should stress more that, were the PGT-M already planned for an existing and known familial disorder, the number of embryos required for (extended) selection must increase and the chances to have suitable embryos would reduce. So, although ECS has the potential to enhance their reproductive autonomy, it has also the potential to reduce their chances to have a child. In the scenario where PGT-M would be coercively offered, this might be problematic.	Based on this comment and further reflection, we have added a sentence in the paper on expectation management and residual risks.
Francesca Forzano	General comment - 7		The arguments are very well discussed, but a summary through a table or a grey box would be helpful for the reader.	We have summarized all recommendations in the last section "Conclusions and recommendations". We will consider a summary table if this is in line with the editorial policies of HROpen,
Francesca Forzano	General comment - 8		The suggestion of embedding ECS in "rigorous research protocols", without exemplifying targets of such protocols remains somewhat "cloudy". Suggestions on items to collect and monitor would be helpful. Would ESHRE consider a centralized database for such researches?	ESHRE is considering a technical paper on the same topic, which would include more technical and practical details on research to be performed. This is outside the scope of the current paper.
Francesca Forzano		110	"Over the past two decades, more than 1300 recessively inherited (autosomal or X-linked) mutations" should be changed to "Over the past two decades, more than 1300 recessively inherited (autosomal or X-linked) genetic disorders".	We have adapted "mutations" to "disorders" as suggested by the reviewer.
Francesca Forzano		538 - 540	A serious but avoidable health problem could also be a good reason for testing, even if reproductive options are not at stake. E.g. MCADD, G6PD deficiency.	After discussion, it was decided not to emphasize this option in the paper, considering the presumed benefit would be very rare.
Francesca Forzano		588 - 594	NBS aims to avoid some of the irreversible health problems due to these conditions (CF, HbPs), but still many remain. For those NBS conditions (inborn errors of metabolism) where several infants die before the NBS result is communicated, or where the majority of health damage cannot be avoided after NBS, we would argue that it could be proportionate to also add the condition to ECS. See for instance Kirk et al EJHG 2020 (https://doi.org/10.1038/s41431-020-0685-x)	The text has been amended as suggested by the reviewer.
Francesca Spinella	General		We appreciated and praised the effort of the ethics group in providing such useful document. This is a comprehensive examination of the ethical and moral aspect in implementing ECS to MAR applicants. In particular, we concordantly support the critical role of information and of pre- and post-genetic counselling to ensure an autonomous reproduction choice to patients. As a scientific society engaged in the field of human reproduction and interested in the definition of the criteria for the application of ECS in MAR patients we propose the following suggestions:	Thank you
Francesca Spinella	2	52	Please add more detail on definition of class variants (not only 4 and 5);	The information on class 4 and 5 variants is included further in the text (not in the abstract). The paper reads "Whereas class 4 variants have a high likelihood of

				being pathogenic, class 5 variants are considered to be definitely pathogenic."
Francesca Spinella	6	235	For risk calculation it should be also mentioned the importance to evaluate the incidence and frequency of each specific genetic disease too. Please add some comment on that in the text;	The Ethics Committee. really doubts whether this is necessary, given the Ethics perspective of this manuscript. After discussion, the Committee agrees that no general recommendations or risk calculations can be provided, as they would need to consider local prevalence of the disorder, and/or specific genetic variants.
Francesca Spinella	General		We also suggest that the informed consent for ECS should be integrated in the general one. On this regards, we suggest to add some additional information regarding the criteria for genetic risk calculation	We consider this to be both cryptic and of secondary importance - this document is about the normative framework of ECS in ART,