December 2022

ESHRE Add-ons Working Group

ESHRE Good practice recommendations for add-ons in reproductive medicine

European Society of Human Reproduction and Embryology

REVIEW REPORT

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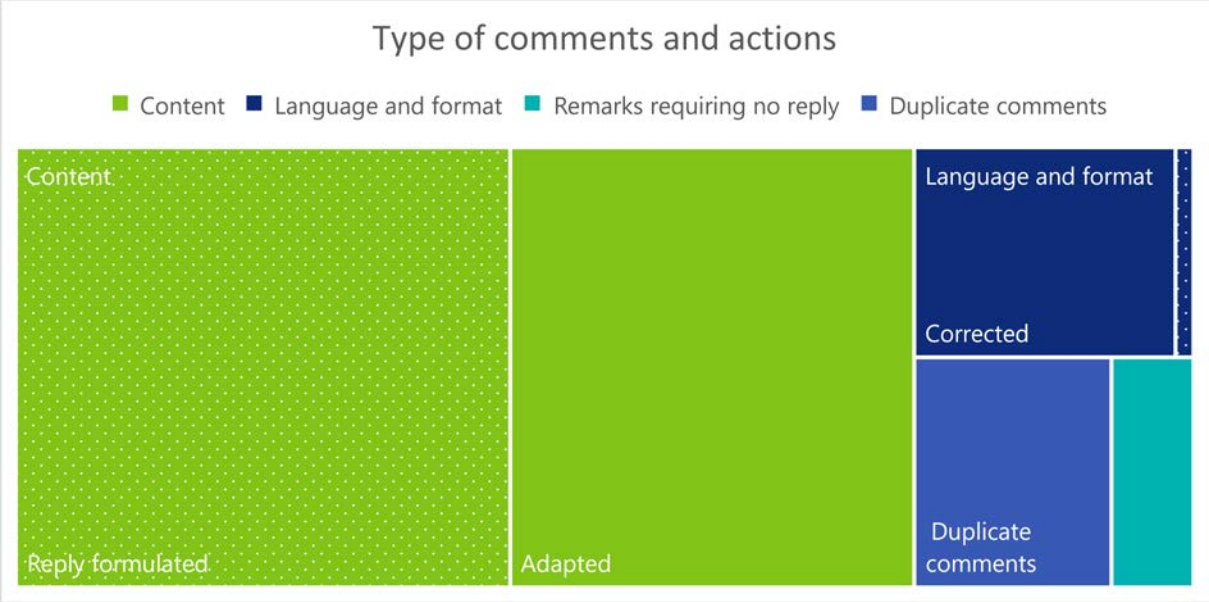
The draft of the paper "ESHRE Good practice recommendations for add-ons in reproductive medicine" was published for public review for 4 weeks, between 1 November and 1 December 2022.

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

During the stakeholder review, a total of 274 comments (including 24 duplicates) were received from 46 reviewers. Reviewers included professionals and representatives of donor-conceived offspring organisations.

The comments were focussed on the content of the guideline (209 comments), language and style (31 comments), or were remarks that did not require a reply (10 comments). All comments to the language and format were checked and corrected where relevant.

The comments to the content of the paper (n=209) were assessed by the working group and where relevant, adaptations were made in the paper (n=94; 45%). Adaptations included revisions and/or clarifications of the text, and amendments to the recommendations. For a number of comments, the working group considered them outside the scope of the paper or not appropriate/relevant (n=115; 55%).



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
Hungarian Human Reproduction Society **Versys Clinics Human Reproduction Institute**	Hungary	Attila Vereczkey
Next Fertility Prof. Zech	Austria	Dietmar Spitzer Maximilian Murtinger Maximilian Schuff
The Evewell (Harley Street) Limited	UK	Christian S Ottolini Teodora Popa Colin J Davis
IVI-RMA Global	Spain, Portugal, Italy, UK	Antonio Requena Vanessa Vergara Nicolás Prados
AGRBM (Arbeitsgemeinschaft Reproduktionsbiologie des Menschen - German Society of German Society of Human Reproductive Biology)	Germany	Verena Nordhoff
Eurofins-Biomnis, France	France	Shubert B.
Vitrolife A/S	Denmark	Tine Qvistgaard Kajhøj
IGENOMIX (Vitrolife Group)	Spain	Carmen Rubio
Vitrolife Sweden AB (Vitrolife Group)	Sweden	Mark Larman

Individual experts

Reviewer	Country
Veljko Vlaisavljevic	
Wellington Martins	
Xavier Vinals Gonzalez	UK
Roy Farquharson	UK
E. Scott Sills	USA
Forest Garner	USA
Jean Calleja-Agius	Malta
Ahmed Samy Saad	Egypt
Pavel Trávník	Czech Republic
Enver Kerem Dirican	

Rukhsana Karim	Pakistan
Bryan Woodward	UK
Mete Isikoglu	Turkey
Vivienne Raper	UK
Carlos Calhaz-Jorge	Portugal
Stephan Gordts	Belgium
Zuzana Holubcová	Czech Republic
David Cahill	UK
Arianna D'Angelo	UK
George Pados	Greece
Ainsley Newson, Siun Gallagher, Wendy Lipworth	Australia
Aboubakr Mohamed Elnashar	Egypt
Danilo Cimadomo, Antonio Capalbo	Italy
Ramos Liliana	The Netherlands
Chi Chiu Wang	Hong Kong
J. Smitz	Belgium
Elena Kostova	The Netherlands
Minerva Ferrer-Buitrago	Spain
Cristina Magli	Italy
Tarek El-Toukhy	UK
Ahmed Fawzy Galal	Egypt
Alan Thornhill	UK
Christos Venetis **Efstratios Kolibianakis**	Australia Greece
Sarah Lensen **Andy Vail** **Jack Wilkinson**	 Australia UK
Sophie Petropoulos	Sweden
Josie Hamper	UK
Maria Jose De los Santos	Spain

Reviewer comments and replies

Reviewer	Page	Line	Comment	Action / Reply
INTRODUCTION				
Cristina Magli	/	/	I understand the difficulty of this topic, but the feeling that I have when reading this section, is of a negative position regarding add-ons. I would like to be mentioned that innovations are coming at a fast rate and that we have the duty of aiming at improvement in our clinical practice. The proper introduction of some add-ons may actually result in the future in a real advantage for the patients, especially for some categories of patients. The difficulty is to realize proper studies with well defined patients' categories and primary outcomes. I also would like to see a difference in the recommendations when dealing with add-ons that have safety issues (i.e. mitochondrial replacement therapy) versus those without a (currently) proven advantage (i.e. sperm fragmentation test). Similarly, there is a difference between techniques with RCTs providing low level of evidence (i.e. antioxidant therapy) vs. those where no data are available (i.e. niPGT).	The working group acknowledges this in the discussion. An overview of the supporting evidence behind the recommendations, both for efficacy and safety can be found in annex II.
Cristina Magli	/	/	in the Introduction or in the Discussion, a comment should be made regarding the introduction of a specific add-on in the clinical practice after a specific risk-assessment.	A sentence was added to the discussion.
Carmen Rubio	/	/	We would appreciate if it could be clarified what are the criteria to define adds-on.	As specified in the introduction, in this recommendations paper, treatment add-ons are defined as beyond conventional for an IVF/ICSI cycle and thus optional additional procedures that are sometimes offered on top of standard fertility procedures.
Carlos Calhaz-Jorge	2	49	1978 was the year of the first baby born after IVF, not of the first application	This was corrected in the text.
Danilo Cimadomo Antonio Capalbo	2	50-71	We think that at least the mean maternal age of the patients these percentages apply to are needed	The mean age from the EIM data report is not known. Data is collected by age category.

Bryan Woodward	2	51 (and throughout)	Suggest changing the term “IVF to “IVF treatment,	This was adapted as suggested.
Carlos Calhaz-Jorge	2	55	The reference to the EIM report published in 2021 is misleading. All the numbers provided in the text come from the report published in 2022	We have corrected the reference.
Carlos Calhaz-Jorge	2	59	I suggest “… The EIM report mentions an estimated cumulative delivery …”	This was adapted as suggested.
Carlos Calhaz-Jorge	2	59	“… delivery rate of 32.3%, calculated over all cycles, calculated as the…”. Please delete the highlighted text	This was adapted as suggested.
Carlos Calhaz-Jorge	2	68	Suggestion: to add the word cumulative in the sentence “Belgian registry data similarly showed a cumulative LBR of…”	This was adapted as suggested.
Carlos Calhaz-Jorge	2	69	Suggestion: to add the word multinational in the sentence “A multicenter, multinational, study reported a …”	This was adapted as suggested.
Carlos Calhaz-Jorge	2	72	Suggestion: “The cumulative rate per one complete treatment…”	The sentence was adapted.
Elena Kostova	2	76	Typo – date should be data	This was corrected in the text.
Carlos Calhaz-Jorge	2	77	The last sentence of this paragraph is followed by two references. Due to the content of the sentence it is difficult to understand	We have corrected the reference.
Ramos Liliana	2	77	Typo: 2 references under 1 bracket …..2021) (Malchau et al 2017)	We have corrected the reference.
Mete Isikoglu	2	77	An extended population based study by Li et al revealing cumulative live birth rate following ICSI cycles compared with IVF cycles for couples with non-male factor infertility may worth to be mentioned while giving the cumulative birth rate of ART (Li Z, Wang AY, Bowman M, Hammarberg K, Farquhar C, Johnson L, Safi N, Sullivan EA. ICSI does not increase the cumulative live birth rate in non-male factor infertility. Hum Reprod. 2018 Jul 1;33(7):1322-1330. doi: 10.1093/humrep/dey118. PMID: 29897449.)	Even though this is a very large observational study, higher quality evidence was included in the ICSI section. Nevertheless, the conclusion of the RCTs and this observational study is the same.
Carlos Calhaz-Jorge	2	78	Propose to remove the word “However” that started the sentence.	This was adapted as suggested.
Alan Thornhill	2	80	1. The Introduction section needs more balance with respect to the incidence of patients dropping out after failing IVF cycles. This is one of the reasons why patients seek additional treatment options and, as such, it cannot be simply an aside in this comprehensive review. One might say ‘doing nothing (different) isn’t necessarily free’. There are a number of good papers describing IVF dropout rates after multiple rounds of unsuccessful IVF. I believe they should be properly referenced here as part of the rationale as to why patients seek additional treatments on top of basic or routine IVF.	References were added to the introduction.
Bryan Woodward	2	81	Why specifically mention clinicians? Perhaps replace with “Healthcare professionals”	This was adapted as suggested.

Zuzana Holubcová	2 and 45	85 and 1770	terminology/wording Do not define adds-on as „not clinically relevant“ Better describe them as non-essential, optional, additional, or beyond conventional procedures... I also disagree with phrasing that adds-on „should not be offered to patients“ please distinguish between offered - advertised to all patients and offered = going an extra mile, doing our utmost when the conventional approach failed.	The WG agreed to change to "supplementary options" and revised the wording of the recommendations.
Mete Isikoglu	2	85	It may be more accurate to substitute the expression “…. not clinically relevant…” with “…not mandatory…” or “…not essential…”	The WG agreed to change to "supplementary options"
Alan Thornhill	2	85	2. As with a growing body of literature and commentary on this topic (so-called ‘add-ons’) it seems that scientific hypothesis-driven method is somewhat sidelined in favour of seeking evidence to support the contention that “treatment add-ons are defined here as NOT BEING CLINICALLY RELEVANT for an IVF/ICSI cycle” (Page 2, line 85). I am not sure I understand the purpose of dressing this up as a scientific review when that sentence suggests that the authors have already made up their minds (before conducting the review and presenting the evidence.	This recommendations paper has been developed according to the manual for development of ESHRE good practice recommendations, as stated in the methods section. The WG has agreed to change to “supplementary options” to define add-ons.
Alan Thornhill	3	92	3. There is a general lack of references supporting some of the claims in the introduction (e.g. (i) ‘the uptake of add-ons is estimated to be lower...’ (page 3, line 92). (ii) ICSI is used in all cycles (page 3, line 97). These claims are stated as facts.	A reference was added to the text.
Mete Isikoglu	3	98	As expressed in page 3 line 98, ICSI should be considered as an add-on when used in non-male factor cases. As the most overused add-on treatment (in non-male factor infertility), ICSI should definitely take place as a crucial topic in this utmost valuable guideline.	Thank you, the working group agrees with the reviewer.
Ramos Liliana	3	101	Change “The paper…” for This paper…	This was adapted as suggested.
METHODS				
Carmen Rubio	/	/	There must be explained and published a clear, objective, and measurable criteria to recommend or not each theme.	When formulating recommendations, not only the quality of the available evidence needs to be taken into account, but also benefits versus harms, patients perspective, health system perspective and the resource use. Therefore, different recommendations may be formulated for different topics, even though the evidence is from a similar quantity and quality.

Alan Thornhill	/	/	5. The methodology section should also define how the 'safety' and 'recommendation' sections for each treatment are established. They appear to be written by different authors as they lack any consistency and this, once again, reads more like opinion (rather than robust review, analysis and synthesis). I will use just a few examples to illustrate this point but the list is exhaustive. If the document is intended as a guideline to aid clinicians and healthcare providers in making decisions about what they should and should not offer as part of their practice it should be able to provide a standardised executive summary for each treatment. It clearly does not achieve this. Example category 1 (safety): (i) page 14, line 569: 'Safety of rescue IVM is questionable' – what does this mean? Do it with caution, don't do it? (ii) page 13, line 500-504. What is the conclusion? Is it neither safe nor harmful – more data required?. I suggest using a simple guide to prevent individual interpretation of the readers of these guidelines. (iii) page 16, line 617 'No safety issues have been reported – this is very clear! (iv) page 18, Line 729 – 'No safety issues have been shown' – It might seem trivial and like 'splitting hairs' but an internationally read and recognised guideline should use standardised language to avoid alternative interpretations or misinterpretations simply because of the use of different words to (possibly?) say the same thing. I have listed 4 examples to illustrate this inconsistent language but there are many ore examples and, I trust, that this can be rectified in the final draft. Example category 2 (recommendation)> as with the above examples of inconsistent language for 'safety' the same appears to be true of the 'recommendation' category. Again, there is a long list of examples but to highlight just a few: (i) page 24, line 929: 'routine use of PGTA is not recommended' – please define 'routine' in methodology (see above), (ii) page 24, line 931 – niPGTA doesn't even get a recommendation in its own section– it is put in the same section as mitochondrial DNA load measurement – this could be misleading for readers. (iii) page 26, line 995: No clear recommendation (one way or the other) for time-lapse imaging.	The WG has reviewed the safety sections to make them as consistent as possible. The WG has also reviewed the formulation of the recommendations and has now used 4 standard phrases.
Rukhsana Karim	3	/	Indeed this topic is the need of the day. 1- The document is very lengthy and the recommendations should be summarized at the end so as to make it more reader friendly. 2- The target audience is not clearly defined. 3- The conflict of interest not declared. 4- The recommendations and evidence should be graded and classed 5- The date of expiry/next update should be clearly written	This recommendations paper was developed according to the manual for development of ESHRE good practice recommendations, as stated in the methods section. The conflict of interest will be added to the published version of the paper. The GRADE of the evidence can be found in Supplementary materials II.
Arianna D'Angelo	3	/	specify which population the paper is focusing on. Is it general fertility population or patients who have already experienced RIF? The latter are usually more subjected to the offer of adds on and some of the adds on might be appropriate for them I.e. hysteroscopy.	The paper included all infertility populations. If data were specific to a patient population, this was specified in the text. A sentence was added to the methods section.

Alan Thornhill	3	/	4. In the methodology section I believe it is extremely important to make it very clear that when a treatment 'add-on' is not recommended for routine use that does not necessarily mean that it has no value at all or is harmful. It should mean what it says: that it might not be optimal, cost-effective or in all patients if performed for all patients. This could be stressed or explained in a little more detail in this introductory section. It is misleading and potentially harmful to a subgroup of patients who might benefit from a specific non-routine treatment if they are led to believe (even unwittingly) that the specific treatment in question could have no benefit for them. In my opinion, the UK's fertility regulator (HFEA) made a similar move to effectively 'outlaw' specific treatment 'add-ons' (for example PGTA) when they have privately acknowledged that it might be useful in specific categories of patients. Indeed, if it was universally harmful, ineffective and simply a financial burden on patients it would appear to be a huge conflict of interest in licensing it. Thus, PGTA appears to be implicitly accepted by the HFEA but only for specific indications. This is not the 'high level' message a patient received from a 'red traffic light'. Red usually means: stop, do not enter, or harmful.	The WG doesn't see the need to add such explanation to the introduction or methods section. If an intervention is not routinely recommended, but can be considered for a specific population, this is described in the recommendation.
Arianna D'Angelo	3	108	Reference: (Vermeulen, et al., 2019) is missing	We have corrected the reference.
Sarah Lensen Andy Vail Jack Wilkinson	3	109	"A working group was composed of experts in reproductive medicine ensuring variation in clinical and laboratory expertise, and geographical balance." Please clarify if any methodologists were among the working group.	There were two methodologists involved in the development of this recommendations paper. We have added this to the methods section.
Danilo Cimadomo Antonio Capalbo	3	119	Please better define "where relevant". How did you choose that an observational study was either "relevant" or "not relevant"?	In the presence of RCTs, observational studies were only included if the population under study was different from the population in the RCT (s).
Sarah Lensen Andy Vail Jack Wilkinson	3	119	The rationale for, and use of, observational evidence is unclear. - Line 119 "Where relevant data from observational studies were added as well" – when and how was this deemed relevant? The flowchart in the ESHRE guidelines implies observational studies will only be included if RCTs do not exist, however observational studies have been referenced for many of the add-ons.	In the presence of RCTs, observational studies were only included if the population under study was different from the population in the RCT (s).
Danilo Cimadomo Antonio Capalbo	3	121	"(cumulative) LBR" is unclear. LBR and cumulative LBR are two deeply different outcomes. Moreover, you should specify the denominator. Is it per ET (SET or multiple; cleavage or blastocyst; untested or euploid), per ITT, per OPU?	Cumulative live birth rate is the critical outcome for this recommendations paper. However, this outcome is not often reported in clinical studies, therefore live birth rate is used as a surrogate critical outcome.
1. HYSTEROSCOPY				
Carlos Calhaz-Jorge	4	132	Although sometimes not successful, I suggest to remove "attempt for" from the sentence "Screening hysteroscopy refers to the attempt for direct visualization…"	This was adapted in the text.

Carlos Calhaz-Jorge	4	139	"The participants were a mixture…"	This was corrected in the text.
Sarah Lensen Andy Vail Jack Wilkinson	4	144	"There was a borderline significant benefit of hysteroscopy with respect to miscarriage rate (RR 1.01; 95% CI 0.67 to 1.50; 3 RCTs; n=1669; I^2=0%; low quality evidence) (Kamath, et al., 2019)." This result is not of borderline significance or even close to it; the p-value here is p=0.98 (taken from the review).	This was corrected in the text.
Elena Kostova	4	144	I wasn't sure what the authors meant with "There was a borderline significant benefit of hysteroscopy with respect to miscarriage rate (RR 1.01; 95% CI 0.67 to 1.50; 3 RCTs; n=1669 ". According to a publication in BMJ (https://www.bmj.com/content/343/bmj.d3340): "Borderline P values can occur when there is a clinically meaningful treatment effect but a large or moderate standard error—often because of an insufficient number of participants or events (the trial is referred to as being underpowered). This is perhaps the most common cause of borderline results." Looking at the result, the statement about borderline significance seems incorrect.	This was corrected in the text.
Stephan Gordts	4	147	I have no access to the complete paper of Ben Abid 2021. Looking at the patient compliance of hystereoscopy it is important to evaluate the size of the used hysteroscope and if hysteroscopy is performed using a watery dissension medium and not CO2. Info you can find on the paper of Campo et al in Hum reproduction Update 1999, vol 5..	In the paper by Ben Abid 2021, all procedures were done by vaginoscopy using a 2.9 mm diameter hysteroscope (26120 BA STORZ). The WG agrees that the frequency and severity of pain might change with regard to the diameter of the endoscope, experience of the operator and the preference of distension medium or Co2. A sentence was added to the paper.
Stephan Gordts	4	150	The aim of the paper of El Thouky was to evaluate if an hysteroscopy performed the cycle preceeding an IVF cycle will increase the pregnancy rate. The conclusion was that there was no effect, but from this study one cannot conclude that performing an hysteroscopy before referring patient to an IVF program is not beneficial	The WG does not agree with this remark. The available data does not support beneficial effect of performing hysteroscopy before referring patient to an IVF program. This is particularly true when there is lack of any abnormality with ultrasonography or hysterosalpingography. That is the main reason while preferring the phrase of "screening" in the current guideline.
2. ENDOMETRIAL RECEPTIVITY TESTS				
Carlos Calhaz-Jorge	5	178	Suggestion: to remove the word "principal" form the sentence. As it is it suggests that we know some mechanisms apart the principal ones	Adapted as suggested by the reviewer.

Carmen Rubio	5	189	The authors only mention two papers showing benefit after using Endometrial Receptivity testing are mentioned, but there are some more papers showing these positive conclusions that should be included and considered for the recommendations: The endometrial receptivity array for diagnosis and personalized embryo transfer as a treatment for patients with repeated implantation failure. Ruiz-Alonso M, Blesa D, Díaz-Gimeno P, Gómez E, Fernández-Sánchez M, Carranza F, Carrera J, Vilella F, Pellicer A, Simón C. Fertil Steril. 2013 Sep;100(3):818-24. What a difference two days make: "personalized" embryo transfer (pET) paradigm: a case report and pilot study. Ruiz-Alonso M, Galindo N, Pellicer A, Simón C. Hum Reprod. 2014 Jun;29(6):1244-7. Live birth after embryo transfer in an unresponsive thin endometrium. Cruz F., Bellver J. Gynecol Endocrinol. 2014; 30(7):481-4. Endometrial receptivity array: Clinical application. Mahajan N. J Hum Reprod Sci. 2015 Jul-Sep;8(3):121-9. Different Endometrial Receptivity in Each Hemiuterus of a Woman With Uterus Didelphys and Previous Failed Embryo Transfers. Carranza F, González-Ravina A, Blasco V, Fernández-Sánchez M. J Hum Reprod Sci. 2018;11(3):297- 299. Why results of endometrial receptivity assay testing should not be discounted in recurrent implantation failure? Simrandeep K., Padmaja N. The Onco Fertility Journal. 2019; 2(1): 46-49. The Reproductive Outcomes for the Infertile Patients with Recurrent Implantation failures May be improved by Endometrial Receptivity Array Test. Ota, T., Funabiki, M., Tada, Y., Karita, M., Hayashi, T., Maeda, K. et al. Journal of Medical Cases. 2019; 10(5), 138-140. Personalized Embryo Transfer Helps in Improving In vitro Fertilization/ICSI Outcomes in Patients with Recurrent Implantation Failure. Patel JA, Patel AJ, Banker JM, Shah SI, Banker MR. J Hum Reprod Sci. 2019; 12(1):59-66. Endometrial Receptivity Analysis - a tool to increase an implantation rate in assisted reproduction. Hromadová L; Tokareva I; Veselá K; Trávník P; Veselý J. Ceska Gynekol. 2019; 84(3): 177-183. Does personalized embryo transfer based on ERA improve the outcomes in patients with thin endometrium and RIF in Self Versus Donor Programme? Selvaraj P, Selvaraj K, Sivakumar M, Chandrasekar H, Srinivasan V. Journal of Gynecological Research and Obsterics, 6(3), 076-080. Evaluation of Pregnancy Outcomes of Vitrified-Warmed Blastocyst Transfer before and after Endometrial Receptivity Analysis in Identical Patients with Recurrent Implantation Failure. Kasahara Y, Hashimoto T, Yokomizo R, Takeshige Y, Yoshinaga K, Toya M. et al Fertility & Reproduction. 2020; 3(2):35-41. Role of endometrial receptivity array in current implantation failure. Samadhiya R, Swarnkar G, Singh A, Chittawar P. Fertility Science and Research, 8(2), 180. Role of endometrial receptivity array for implantation failure in in-vitro fertilization & intracytoplasmic sperm injection. Nafees R, Khan H, Khan Y, Awais A, Farooqi M, Nissar R. Biomedica, 2021.37(4), 220-226 Comparison of the Effectiveness of Endometrial Receptivity Analysis (ERA) to Guide Personalized Embryo Transfer with Conventional Frozen Embryo Transfer in 281 Chinese Women with Recurrent Implantation Failure. Jia Y, Sha Y, Qiu Z, Guo Y, Tan A, Huang Y. et al Med Sci Monit. 2022;28:e935634. Published 2022 Mar 22. doi:10.12659/MSM.935634. The Clinical Efficacy of Personalized Embryo Transfer Guided by the Endometrial Receptivity Array/Analysis on IVF/ICSI Outcomes: A Systematic Review and Meta-Analysis. Liu Z, Liu X, Wang M, Zhao H, He S, Lai S. et al Front Physiol. 2022;13:841437. Identifying women with a narrow window of embryo implantation using the endometrial receptivity assay. Rose B. International Journal of Clinical Obstetrics and Gynaecology 2022; 6(3): 52-54. Specifically, it would be worth mentioning the two more recent publications related the use of Endometrial Receptivity testing on RIF populations: Jia et al 2022, comparing RIF patients with and without endometrial receptivity test, showing a significant increase in the reproductive outcome when transfer was performed according to the results of the test. On the other hand, Rose 2022, showed that patients with several	4/16 of the suggested studies are case reports and are not qualified to be included in the presence of higher quality evidence, 5/16 of the suggested studies are published in a journal not indexed for Pubmed and thus not qualified to be included. 3 of the suggested cohort studies are included in the MA by Craciunas et al 2019. The MA by Liu et al was excluded by the WG because it combines observational and and RCT data and does not rate data in terms of quality. Jia et al 2022 seems to include the same patients as Jia et al 2021 which was included in the paper.

			implantation failures, got pregnant in high proportion when adjusting the progesterone timing according to Endometrial Receptivity Evaluation.	
Carmen Rubio	5	190	The authors mention a review, that finally was not conducted as meta-analysis. However, the meta-analysis from Lui et al 2022 it is not mentioned. This meta-analysis concludes that using ERA in the RIF population in which poor outcomes are expected, the clinical outcomes can improve and reach the values of good prognosis patients. This reinforces the fact that endometrial receptivity is helping RIF population. The Clinical Efficacy of Personalized Embryo Transfer Guided by the Endometrial Receptivity Array/Analysis on IVF/ICSI Outcomes: A Systematic Review and Meta-Analysis. Liu Z, Liu X, Wang M, Zhao H, He S, Lai S. et al. Front Physiol. 2022;13:841437.	The MA by Liu et al was evaluated by the working group, however, it was not included because it combines observational and RCT data and does not rate data in terms of quality.
Mete Isikoglu	5	195	Very recent multicentre retrospective study from the same group revealed lower cumulative and per transfer live birth rate during donor and autologous cycles when ERA test was used in RIF cases (Cozzolino M, Diáz-Gimeno P, Pellicer A, Garrido N. Use of the endometrial receptivity array to guide personalized embryo transfer after a failed transfer attempt was associated with a lower cumulative and per transfer live birth rate during donor and autologous cycles. Fertil Steril. 2022 Oct;118(4):724-736. doi: 10.1016/j.fertnstert.2022.07.007. Epub 2022 Sep 6. PMID: 36070983.). It may worth to mention this study to emphasize the final comment on ERA test.	This is a decently carried out study even if retrospective. A sentence was added for completeness, although it does not change the final conclusion.
Carmen Rubio	5	196	In the comments about the paper of Simon et al 2020, the results of the per protocol analysis are not included. Considering that Endometrial Receptivity testing is not a treatment itself, but a test that needs a proper application of the recommendation in order to reproduce the obtained result, it makes sense to give credit to the per protocol analysis (when the recommendation given in the report is properly applied in the transfer cycle). The per protocol analysis reinforce the idea of a significant increased Implantation and pregnancy rates when personalization of ET is done, and recommendations applied.	A basic principle of all RCTs is the analysis per intent to treat in order to preserve the prognostic balance afforded by randomization, thereby minimizing any risk of bias that may be introduced by comparing groups that differ in prognostic variables. Per definition patients will be offered to perform the test without knowing if the results is receptive pre-receptive or post receptive. If performing the test does not increase the chances of pregnancy in the intent to treat analysis it should not be recommended

Carmen Rubio	5	199	The criticisms to Simon et al 2020 RCT are detailed, but not the answer from the authors (in order to avoid bias, this answer should have been included): Response to: Comments on the methodology of an endometrial receptivity array trial. Simón, C., Gomez, C., Ruiz, M., Mol, B. W., & Valbuena, D. Reproductive BioMedicine Online 2021;42(1), 284. Endometrial Receptivity Analysis (ERA): data versus opinions. Ruiz-Alonso M, Valbuena D, Gomez C, Cuzzi J, Simon C. Hum Reprod Open. 2021 Apr 14;2021(2):hoab011.	A basic principle of all RCTs is the analysis per intent to treat in order to preserve the prognostic balance afforded by randomization, thereby minimizing any risk of bias that may be introduced by comparing groups that differ in prognostic variables. Per definition patients will be offered to perform the test without knowing if the results is receptive prereceptive or post receptive. If performing the test does not increse the charnces of pregnancy in the intent to treat analysis it should not be recommended
Carlos Calhaz-Jorge	5	203	Suggestion: to add “positive” in the sentence “...which proved to have a larger, positive, effect on implantation rate…”	This was adapted as suggested.
Arianna D'Angelo	5	205	add info on pain during pipelle biopsy ; there are many papers on endo scratch (which is similar) showing that it is painful.	Adapted as suggested by the reviewer.
Carmen Rubio	6	209	Given all the evidence above mentioned, supported by several publications, it should be considered to modify the recommendation for Endometrial Receptivity tests to: Given the clinical outcome reported for RIF population after using Endometrial Receptivity Testing, it could be considered specifically for RIF population in which other factors have been previously discarded.	Based on the latest available evidence and the latest largest RCT (Doyle et al., 2022), outnumberring all available evidence from retrospective studies, the recommendation should remain the same.
Cristina Magli	6	210	“Due to the lack of clear benefit”. I would say, “Due to the lack of robust data”.	Adapted as suggested by the reviewer
Arianna D'Angelo	6	212	to add that it is painful for the patient	Adapted as suggested by the reviewer.
3. REPRODUCTIVE IMMUNOLOGY TESTS AND TREATMENTS				
George Pados	6	213	The role of B2GPI should, also be examined, since they contribute to APS and are particular important in patients who test negative for other aPL	Thank you for the suggestion. At this stage, this topic cannot be added to the current recommendations paper. However, we will keep it in mind for the update or the extension of the paper.
Jean Calleja Agius	6	215	Addition of testing/measurement of cytokines	Thank you for the suggestion. At this stage, this topic cannot be added to the current recommendations paper. However, we will keep it in mind for the update or the extension of the paper.

Vivienne Raper	6	216	It may be worth adding something to the line about other medical indications to reflect the existence of a cohort of women who have extremely poor health, but no diagnosis, and whose non-fertility health is improved by immune treatment for fertility. The average time to diagnosis with an autoimmune condition (in the US – UK figures I've seen are similar) is 4.5 years (https://www.benaroyaresearch.org/blog/post/diagnosing-autoimmune-diseases). And there are a wide range of poorly-understood immune-related conditions, as well. The average age of onset for autoimmune conditions is often during the reproductive years (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3238350/) and around 80% of people with autoimmune conditions are female (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7292717/). This is suggestive of a significant minority of women with undiagnosed autoimmune and immune-linked diseases. The abnormalities caused by these diseases often show up on the NK and TH1/TH2 tests. Most of the studies I've read say there aren't clear links between fertility and many autoimmune diseases, but – obviously – women need to have a diagnosis to appear in those studies. This, in turn, means that they have a treatment plan in place. There are no studies I've found showing the impact of having an undiagnosed/untreated autoimmune disease on fertility – it wouldn't be ethical to do that study, I assume. I was off work with an undiagnosable disease, which I believed was a combination of depression and repeat serious gym injuries for four years before trying Humira for fertility treatment. It was a revelation to me as it accidentally treated my disease (I fell pregnant a few months later naturally). This has helped enormously with the diagnosis, management and treatment of my condition subsequently (I still have no clear diagnosis, although it's assumed to be an autoinflammatory condition). I now advise women on fertility forums to only consider immune treatment if they have symptoms of a disease. It is very obvious through reading anecdotal accounts that the 'miracle pregnancies' using immune treatment are all women with a constellation (often) of poorly treated or undiagnosed autoimmune (usually) disease who find their fertility is improved by someone throwing medication at it. This is unfortunate, as it reflects failings in the wider NHS to diagnose and treat autoimmune disease properly, especially where the symptoms are vague (e.g. pain, fatigue) or don't generate clear diagnostics through blood tests (e.g. sero-negative autoimmune disease). There is a separate, again poorly understood, link between endometriosis (which I have) and autoimmune diseases (e.g. https://pubmed.ncbi.nlm.nih.gov/31260048/). Endometriosis being a disease, again, that is poorly understood and seriously underdiagnosed despite it being a leading cause of infertility. Again, with me, who has found I have endometriosis aged 42, it's obvious that early-stage endometriosis generates inflammatory symptoms (in fact, flares of my inflammatory disease around my period have been the ONLY symptom of endo for me for decades). Again, I would expect there to be a cohort of women who benefit from immune treatment purely because they have undiagnosed early-stage endometriosis (this is clearly the case for me). I would not know I had severe endometriosis if I was not undergoing reproductive immunology, simply because the symptoms of my uncontrolled immune flares (e.g. low-grade fevers, severe joint and muscle pain) overwhelm all possible classic symptoms of endo. In summary, there are women with medical indications for immune-related diseases who are not taking medication for them already, simply because they haven't been diagnosed! This is scandalous, but it does need to be mentioned. As autoimmune immune diagnoses often occur in groups, with women having several conditions simultaneously, there's an obvious ongoing research question about the extent to which you should check for endometriosis in women with autoimmune diseases and, vice versa, in women with immune symptoms. So, quite nuanced, but I think there needs to be a quick mention of the existence of some number of people with general health symptoms indicative of undiagnosed immune-linked disease – not just those who are already diagnosed and on medication.	Thank you for sharing your story. However, administering treatment without confirmation of a positive (or abnormal) test, also called empirical treatment, is not supported by evidence from clinical studies and generally not advisable.

Arianna D'Angelo	6	218	you might want to add the reference to a different ESHRE guideline which is covering these category of women being the RPL guidelines	For the immune section, we have identified a specific patient population where there might be a benefit of testing or treatment. Therefore, there is no need to cite the RPL guideline here.
Ramos Liliana	7	252	Add a recommendation for Immunological test	The recommendation on immunological diagnostic tests can be found at the end of the section.
Carlos Calhaz-Jorge	7	267	I suggest to rephrase the sentence. The high risk of pre-eclampsia is for oocyte recipients, not donors. And it's reasonable to think that this high risk is related with the advanced maternal age of those women.	This was corrected in the text.
Arianna D'Angelo	7	270	to add at the end " on the paper".	This was corrected in the text.
Arianna D'Angelo	7	273	remove "and"and put commas instead	This was corrected in the text.
George Pados	7	277	The role of immune modulation treatments which include administration of corticosteroids, aspirin e.t.c should also be highlighted	These topics are covered in other sections of the paper.
Carlos Calhaz-Jorge	7	291	Maybe better to explain the meaning of "LIF". Not included in the list of abbreviations	This was corrected in the text.
Carlos Calhaz-Jorge	8	309	"..a range of immune" instead of "..a range on immune"?	This was corrected in the text.
Carlos Calhaz-Jorge	8	313	Maybe better to explain the meaning of "LIF". Not included in the list of abbreviations	This was corrected in the text.
Dietmar Spitzer Maximilian Murtinger Maximilian Schuff	6-8	213-314	Seeing that diagnosing chronic endometritis by immunohistological testing of endometrial biopsies is raising this subchapter urgently needs also positioning in regard to endometrial biopsies for testing plasma cells as an indicator for plasma cells.	Thank you for the suggestion. At this stage, this topic cannot be added to the current recommendations paper. However, we will keep it in mind for the update or the extension of the paper.
4. ARTIFICIAL OOCYTE ACTIVATION (AOA)				
Minerva Ferrer-Buitrago	8	/	I like to thank the authors for approaching the responsible applicability of AOA in the clinic. Please, find my comments below for your kind consideration.	Thank you for these kind words.

Ahmed Samy Saad	8	316	Strontium Has a role in oocyte activation but only ionomycin or calcimycin has been discussed.	The text states that "the most common ones being Ca2+ -ionophores such as calcimycin or ionomycin". The WG did not exclude strontium chloride and all the other compounds used. On the contrary, there is evidence that strontium fails to induce Ca2+ release and activation in human oocytes (Lu et al., HRO, 2018) which is likely the result of a lower level of ATP in human eggs (Storey et al., 2021, MHR). In mice strontium works well.
Bryan Woodward	8	318a nd 332	Replace “storages” with “stores”	This was adapted as suggested.
Minerva Ferrer-Buitrago	8	324	To contextualize the different nature of the Ca2+ signaling after using Ca+2 ionophores (single Ca2+ transient) and the one observed during fertilization after ICSI (repetitive Ca2+ oscillations) it would be interesting to include a reference to this work: https://doi.org/10.1093/humrep/dex376 The authors described the oscillatory Ca2+ signaling patterns in human oocytes after ICSI following fertilization with control donor sperm and sperm with previous ICSI failures.	The WG acknowledges that this is indeed a key paper. However, it is considered outside the scope of this recommendations paper.
Bryan Woodward	8-9	330	I am not so sure about mentioning the modified ICSI technique. When I troubleshoot ICSI due to low success rates, I still come across embryologists who tell me about the benefit of “aggressive” ICSI. This involves performing v.fast oolemma puncture and aspirating way too much ooplasm after oolemma rupture has taken place. This may increase Calcium levels, but the detrimental resultant disruption of the oocyte ultrastructure outweighs any benefit. This wasn’t the the intention of the cited paper, and this is certainly not the “least invasive” technique.	The paragraph here is indeed slightly confusing because of our attempt to explain this in short. Actually there are 2 modified ICSI techniques described. One is Tesarik et al. (2002), who reported indeed >20% degeneration. Ebner et al. (2004) have chosen a different approach using metabolic active mitochondria in a non-invasive ICSI. The sentence was adapted to clarify.
Zuzana Holubcová	9	347	The application of AOA is described as a simple washing in ionophore-containing media, but the Ghent group (prof. Heidryckx) uses the strategy of direct injection of CaCl2. This approach is said to be more effective. Why it is not mentioned?	This technique was not mentioned because active injection of CaCl2 is not allowed in all countries. This information was added to the Nikiforaki et. Reference, who also used direct injection plus ionomycin.

Xavier Vinals Gonzalez	9	365	Some forms of A23187 are currently CE marked for diagnostic use but not for treatment. CE marking is a certification mark that shows compliance with health, safety, and environmental protection standards for goods sold within the European Economic Area.	The WG only looked at efficacy and safety of the interventions. CE marking is considered outside the scope of this recommendations paper.
Maria Jose De los Santos	9	365	regarding the use of Gynemed's Ca ionophore. This product has CE marking as a diagnostic method, not as a treatment and therefore thre are reasonable doubts that we can treat (not diagnose) oocytes so lightly with this product and transfer the resulting embryos	The WG only looked at efficacy and safety of the interventions. CE marking is considered outside the scope of this recommendations paper.
Carlos Calhaz-Jorge	10	380	Maybe the word “However” at the beginning of the sentence is not needed.	The text in this paragraph is in contrast to the previous one.
Minerva Ferrer-Buitrago	10	380	I share the following reference for your consideration: https://doi.org/10.1093/molehr/gaaa060 The authors compared a series of AOA protocols, which induced distinct Ca2+ pattern signaling (single and oscillatory) in a PLCz-KO mouse model. As a result, they did not find any significant difference in the transcriptional gene profile at blastocyst stage in any of the AOA methods compared to the control ICSI group.	This reference falls outside the scope of this recommendations paper. Nevertheless, the work of Ferrer-Buitrago et al. is highly appreciated by the WG.
Arianna D'Angelo	10	384	is there any risk of allergic reaction in women allergic to these antibiotics? Should we mention this aspect under safety concerns?	Good question, however, the ionophores do not enter the oocyte, and they are washed off after usage.
Bryan Woodward	10	390	Suggest replacing “although this makes sense” with “although this may make sense”, as it is controversial.	This was adapted as suggested.
Minerva Ferrer-Buitrago	10	392	I would suggest including a reference to the use of rPLCz as the only potential AOA alternative in humans to obtain a Ca2+ oscillatory response, as the effect of SrCl2 in the human remains debatable. Here, it is very important to remark the experimental nature of this methodology.	A sentence was added to the section "other aspects".
5. MITOCHONDRIAL REPLACEMENT THERAPY				
George Pados	11	416	First baby born in Greece using the maternal spindle transfer method as part of pilot trial conducted by the institute of life and embryotools scientific team (Psathas et al., 2020, www.prnewswire.com)	Several websites have announced the birth of babies after mitochondrial replacement. However, we decided not to add these to the paper as they are not peer-reviewed information. We will therefore also not add this link to the website.
Xavier Vinals Gonzalez	11	430	After mitochondrial replacement therapy using a donor egg, it is important to be able to quantify the level of heteroplasmy as there will be some carryover of mutated mitochondria.	This problem is addressed and referenced in the paragraph on 'other aspects', (Kang et al., 2016). Since we are not making recommendations regarding treatment of mitochondrial diseases, this issue is not discussed further.

Zuzana Holubcová	11	432	No recommendation for the avoidance of mitochondrial diseases using spindle/pronuclear transfer. Recommending referral of affected patients to a specialized clinic holding permission for experimental mitochondria replacement therapy would be of consideration. (as far as I know, Newcastle mitochondrial reproductive clinic holds such permission).	Avoidance of mitochondrial diseases is not considered an Add-on by the working group, and therefore no specific recommendation on the practice is given. A sentence is added to the text to make this clearer.
6. IN VITRO ACTIVATION OF DORMANT FOLLICLES (IVA)				
Ramos Liliana	11	435	In vitro activation (IVA) > this is not a lab intervention, but it should be placed under Clinical Management	The initial attempt of IVA consisted of both surgical and laboratory interventions. However, whereas the surgical part was done particularly to induce secondary follicles throughout a few months, the lab interventions aimed to induce dormant primordial follicles within a year. The modified version includes only surgical micro-dissections without any in-vitro activation of follicles. Therefore, it might be better to host this title still in the lab section.
Ramos Liliana	11	436	Add definition for POI in the context of this paper	Studies were included defining the study population as "POI". The WG did not look into the diagnostic criteria used in these studies.
Bryan Woodward	11	438	It might be worth explained the acronyms in full.	These acronyms are better known than the full term, adding this does not provide more clarity.
7. IN VITRO MATURATION (IVM)				
Zuzana Holubcová	12-14	468	This section needs substantial refinement! It does not clearly distinguish between (1) in vitro maturation of oocytes inclosed in preovulatory follicles (non-stimulated cycles, prolonged (24-48 h) culture in the presence of hormones) and (2) rescue in vitro maturation of immature oocytes from stimulated cycles with a suboptimal response (lack of MIIs) and immature oocytes spontaneous extruding PB in vitro on the same day (MI) or overnight (GV). Rescue IVM combined with polarized light microscopy (MII spindle imaging)-guided optimization of ICSI timing has been shown to improve clinical results and give rise to healthy full-term pregnancies in poor prognosis cycles (published evidence is available). This method is now offered by multiple clinics to patients with a small number or no MII oocytes available for ICSI.	In this section, clinical IVM (non- or minimal stimulated cycles) and rescue-IVM (immature oocytes after a suboptimal response to ovarian stimulation) are discussed separately as suggested.

Cristina Magli	12	480	Considering the statements of lines 475-479, the following section about Efficacy should specify which patients category data are referring to (PCOS/high responders or normoresponders).	As specified in the introduction, IVM is not considered an add-on in the case of PCOS or high responders. Included evidence comes from studies with regular cycles.
Ramos Liliana	13	509	Add recommendation for Clinical IVM	The recommendation for clinical and rescue-IVM are the same, so the WG decided not to split-up the recommendation.
Ramos Liliana	13	510	Rescue-IVM Define maturation level of oocytes considered for rescue-IVM (MI oocytes? Or GV?) This “add on ” is incomplete described: define what is meant by “rescue IVM”	A sentence was added to better explain rescue-IVM.
Ramos Liliana	13	519	Typo: correct references divided by brackets	We have corrected the references.
Carlos Calhaz-Jorge	14	537	The clinical pregnancy rates and the LBR are exactly the same. Is it correct? No case of miscarriage?	Correct, this is the data as reported in the publication.
Carlos Calhaz-Jorge	14	564	Maybe better to explain the meaning of “RSM”. Not included in the list of abbreviations	This was corrected in the text.
Carlos Calhaz-Jorge	14	566	I don’t understand the sentence. If no oocyte was obtained (empty follicle syndrome) how a rescue using IVM is possible? And the sentence has two references in spite of referring to just one case	The patient had a history of empty follicle syndrome, and both attempts described in the case report resulted in development of follicles during stimulation, however, only poor-quality, immature oocytes were retrieved at OPU. The sentence describes two cases, hence two references.
Ramos Liliana	14	571	This recommendation is not clear: this technique is for poor responders, but in the Recommendation is suggested for PCOS.	The recommendation states that IVM is not recommended for infertile patients, unless there are specific indications, such as PCOS/high response to OS or fertility preservation
Cristina Magli	14	571	It should be two sets of recommendations, one for “true” IVM and one for rescue-IVM	The recommendation for clinical and rescue-IVM are the same, so the WG decided not to split-up the recommendation.

Bryan Woodward	14	571	Could the recommendation specifically mention both clinical and rescue-IVM, perhaps as two separate recommendations? For the whole section on rescue IVM, the term “immature oocyte” is used; however, could you clarify how many where MI or GV? For MIs that mature to MII, the success rate should be higher (particularly if the IVF lab has a process of checking the time to MII, with more success anticipated in shorter maturation intervals. Also, please can you clarify that t all rescue-IVM cases simply left the Mis/GV oocytes in the same culture medium to mature, rather than supplementing with hormones?	The section on rescue-IVM has been re-written. However, where reported in the detailed studies, information regarding GV or MI status of the immature oocytes was added to the paper. Culture conditions of the immature oocytes were also added to the paper. However, only one paper (Reichman et al., 2010) reported GV or MI origin of the IVM oocytes.
Verena Nordhoff	14	573	Is there any agreed protocol for in vitro maturation of oocytes? Maybe a sentence added here would be helpful.	The protocol for IVM is outside the scope of this recommendations paper.
Maria Jose De los Santos	14	571	regarding rescue IVM (GV rescue), it is not clear in the recommendations if it can be applied or not and under what circumstances since it only mentions IVM in general	The recommendation for clinical and rescue-IVM are the same, so the WG decided not to split-up the recommendation.
8. SPERM DNA DAMAGE TESTING/TREATMENT AND SPERM OXIDATIVE STRESS MEASUREMENT				
Ramos Liliana	15	575	(8) Sperm DNA damage testing: this add-on should be placed under the “sperm evaluation” as this is also by WHO defined as “advanced test”	Actually, sperm DNA damage is distinct from ordinary methods of sperm evaluation. Therefore, it is not feasible to place it under the same heading
Bryan Woodward	15	576	Dor the SDF section, can you add a comment about the recommendation by some teams to perform TESE where a prior report for the man shows high SDF, even though he is normospermic? I have debated this with those that recommend this and always argue primum non nocere! Yet, the practice continues. Can you also consider adding a comment about the recommendations on the reports provided by the labs that provide the SDF assay, which seem to recommend ICSI over conventional IVF, as a way of fixing the problem if high SDF is detected with normospermia. Where is the evidence that ICSI improves success rates in this instance?	A comment was added to the text.
Verena Nordhoff	15	582	Furthermore applying the same test in different labs can result in very heterogeneous results leading to potentially non-comparable values.	Indeed, these points are discussed in the section of "other aspects".

Shubert B.	15	597	A recent longitudinal cohort study involving more than 2500 couples undergoing ART has shown a lower live birth rate (LBR) when SDF > 20% (using SCSA) in standard IVF. Cumulative live birth rates (CLBR) values were higher for the normal group compared with those for the high DNA Fragmentation Index (DFI) values group. No DFI-dependent difference was seen in the ICSI group, suggesting that ICSI should be the best first ART option for these couples (Voncina et al., 2021). Another recent large retrospective cohort study included 1339 couples undergoing 2759 IVF/ICSI cycles found actually similar results. Standard IVF and ICSI cycles were mixed and ICSI was performed > 88% et > 92% in both groups with Sperm DNA Fragmentation (SDF) ≤15% and >15% respectively (using TUNEL assay with flow cytometry). Hence, this study using mostly ICSI reported no significant difference in clinical pregnancy rates and miscarriage rates between both groups. No difference in LBR per embryo transfer were found for the first or for all embryo transfers when comparing sperm DNA fragmentation. And CLBR was not significantly different between groups with high or low SDF (Hervás, et al., 2022). When high sperm DNA fragmentation is found, it is suggested that ICSI should be the first line of treatment. Voncina SM, Stenqvist A, Bungum M, Schyman T, Giwercman A. Sperm DNA fragmentation index and cumulative live birth rate in a cohort of 2,713 couples undergoing assisted reproduction treatment. Fertility and Sterility 2021; 116 : 1483-1489. Hervas I, Pacheco A, Rivera-Egea R, Gil Julia M, Navarro-Gomezlechon A, Garrido N. IVF/ICSI cumulative live birth rates per consumed oocyte remain comparable regardless of sperm DNA fragmentation by TUNEL. Reprod Biomed Online, 2022; 44: 1079-1089.	(1). As there are a few data that represents superiority of advanced sperm selection techniques over ICSI, we did not mention this point with regard to the paper by Voncina et al., 2021. (2).Given the fact that most of the patients had been treated with ICSI in both scenarios (high and normal SDF), it would not be wise to assume that lack of statistical significance for LBR is evidence for the validity of ICSI instead of IVF in patients with high SDF (Hervas I et al., 2022). The authors in that papers do not propose such an assumption either.
Ramos Liliana	15	603	Change ART for MAR	This was adapted as suggested.
Ramos Liliana	16	618	No clear description for the effect of DNA for different MAR techniques: there is difference in CPR between IUI, IVF of ICSI with DNA damaged sperm.	Unfortunately, there is no RCT.
Verena Nordhoff	16	618	Maybe add a sentence that the test renders the tested sperm unusable for ICSI. The DFI value can only be a surrogate for the real sperm population.	A sentence was added to the text.

Shubert B.	16	618	The sentence “Laboratory conditions such as incubation time, centrifugation and cryopreservation (Agarwal, et al., 2020, Zini, 2011), as well as the source of the sperm (ejaculated or processed (Aboulmaouahib et al., 2017, Liu and Liu, 2013), or testicular (Agarwal, et al., 2020)) can significantly influence the results of sperm DNA fragmentation tests.” is confusing as the snap freezing is not considered to modify the result of Sperm DNA Fragmentation (SDF) tests. In the text to be reviewed, sperm cryopreservation is referred to a standard cryopreservation procedure with 1:1 dilution with a cryoprotective agent and then slow freezing. The snap freezing is performed with raw sperm within an hour after sperm collection and is very fast i.e., very different to the conventional cryopreservation procedure. As reported previously, DNA structure is not affected by the snap freezing process on SDF (Evenson et al., 1991) and has shown no effect on SDF with the SCSA and TUNEL assays (Evenson, 1994 and 2002; Sailer et al., 1995; Ollero et al., 2001). Therefore, sperm snap freezing can be used safely for SDF analysis. Evenson DP, Jost LK, Baer RK, Turner TW, Schrader SM. Individuality of DNA denaturation patterns in human sperm as measured by the sperm chromatin structure assay. Reprod Toxicol. 1991; 15: 115-125. Evenson DP, Jost LK. Sperm chromatin structure assay: DNA denaturability. In: Darzynkiewicz Z, Robinson JP, Crissman HA, eds. Methods in Cell Biology. Vol 42. Flow Cytometry. 2nd ed. Orlando, Fla: Academic Press; 1994:159–176. Evenson DP, Larson KL, Jost LK. Sperm chromatin structure assay: its clinical use for detecting sperm DNA fragmentation in male infertility and comparisons with other techniques. J Androl. 2002; 23:25-43. Ollero M, Gil-Guzman E, Lopez MC, Sharma RK, Agarwal A, Larson K, Evenson D, Thomas AJ, Alvarez JG. Characterization of subsets of human spermatozoa at different stages of maturation: implications in the diagnosis and treatment of male infertility. Hum Reprod. 2001; 16:1912–1921. Sailer BL, Jost LK, Evenson DP. Mammalian sperm DNA susceptibility to in situ denaturation associated with the presence of DNA strand breaks as measured by the terminal deoxynucleotidyl transferase assay (TDTA). J Androl. 1995; 16:80–87.	The current sentence aims to describe the heterogeneity among the available studies, does not mainly claim the negative effect of cryo-procedure on SDF. The given references are not relevant with the sentence.

Tarek El-Toukhy	16	628	The recommendation regarding Sperm DNA fragmentation testing that “the routine use of these tests is not recommended outside strict research protocols” should not include the condition “outside strict research protocols” for a number of reasons: firstly, the term “routine use” is not compatible with “strict research protocols” which are far from routine use; secondly the condition “outside strict research protocols” should apply to all other add-ons which could be subject to future research studies, and therefore the condition here is superfluous as it applies to all recommendations and not just Sperm DNA fragmentation testing. Finally, there is a serious concern that adding this condition to sperm DNA fragmentation testing will be used to justify offering the test, since it could be falsely interpreted that it could be offered in some situations and clinics could claim it was offered so that they could review the outcome e.g. retrospectively. The correct and appropriate recommendation should be “the routine use of these tests is not recommended.” Period.	The sentence was adapted.
9. ARTIFICIAL SPERM ACTIVATION				
Zuzana Holubcová	16-17	630	The proposed term is easy to be confused with AOA! „Enhancement of sperm motility“ is better fitting and traditionally used. 636 Pharmacological activation does not „restore“ sperm motility, it only transiently(!) enhances residual sperm motility. Emphasize the effect is short-lasting. I miss literature reference to RCT https://pubmed.ncbi.nlm.nih.gov/34696674/ And case report of a healthy child born after theophylline treatment https://pubmed.ncbi.nlm.nih.gov/33474690/ Is there a reason not to include them?	This is a term also used in literature. No chance to mix it up since it goes with the sperm chapters and "sperm" is not "oocyte". The paper by Azimi et al. was published after the final literature update. More importantly, it is a RCT on oral application of theophylline. Off label with respect to the present paper of us. The work by Holubcova et al (2021) is highly appreciated, however, to show the effect of theo and pentoxyfylline only larger studies, prospective if possible, were taken into consideration. To show that theo and pentoxyfylline do not work in patients with axonemal structure defects case reports had to be used since no-one is doing a prospective study if there is no effect to expect.
Xavier Vinals Gonzalez	17	658	Some forms of theophylline are currently CE marked for diagnostic use but not for treatment. CE marking is a certification mark that shows compliance with health, safety, and environmental protection standards for goods sold within the European Economic Area.	The WG only looked at efficacy and safety of the interventions. CE marking is considered outside the scope of this recommendations paper.
Cristina Magli	17	676	"it should" means that if we do not use the proposed technique, we are doing malpractice?	No of course not. Then it would be a "must"

Xavier Vinals Gonzalez	17	677	Due to the short time period that this chemical has been used in ART, it is important to continuously monitor and track the long term effects and safety of the children born.	Correct. This phrase has been added.
10. ADVANCED METHODS OF SPERM EVALUAION AND SELECTION				
Ramos Liliana	17	678	I suggest to change the title for “Advanced / additional sperm evaluation and selection” Under this section add the DNA damage (8)	The title was changed to "advanced methods of sperm evaluation and selection"
Ramos Liliana	17	688	Change “next step” for method	This was adapted as suggested.
Bryan Woodward	18	696	I stopped considering PICSI when I read the product insert that stated the test should be performed at room temperature. Perhaps this has now changed, but it could be worth checking (and if so, the PICSI dish is being used contrary to manufacturer instructions).	Taken from manufacturer's Instructions for use: "Temperature: Sperm bind best to hyaluronan hydrogel at temperatures below 30°C. At temperatures above 30°C, sperm swimming vigour increases and the swimming force may overcome the binding force. The result is that about one-third of sperm bound at room temperature will show some progressive migration at 37°C and may be deemed not bound, immature. PICSI® Sperm Selection Device dishes placed on a 37°C heated stage will come to about 33°C and then remain at that temperature. At 33°C or even at 37°C, many bound sperm will remain available for selection." A comment was added in the text.
Elena Kostova	18	723	Miller et al 2019 is already included in the meta-analysis for LBR (RR 1.09; 95% CI 0.97 to 1.23; 2 RCTS; n=2903)	This study is indeed included in the meta-analysis. The paragraph was adapted.
Cristina Magli	18	734	I would add “although recent data show an advantage in some categories of patients”.	A comment was added in the text.
Ramos Liliana	19	752	Safety issues: no data about the possibility of using sperm with magnetic beads which has not completely removed after sorting, specially when sorting sperm with ICSI (suggest to add this issue)	The sentence was adapted.
Bryan Woodward	20	802	If the lab is really good at IMSI and uses it as routine, then the process is not so time-consuming. However, where IMSI is not routinely used, the process is time-consuming.	The sentence was adapted.

Sarah Lensen Andy Vail Jack Wilkinson	20 27	783 1047	For PRP, despite multiple (low quality) RCTs suggesting benefit the authors recommend against PRP. Yet for microfluidics, the authors state it "may increase the LBR" based on a single RCT of 128 patients. This trial utilised a commercial test (Fertile Chip) and it's not clear whether the trial was funded by the Chip company. In both cases there is no real safety data. These recommendations therefore appear inconsistent.	The recommendation was adapted. However, for PRP there is significant heterogeneity in application of the method and concentration of the platelets. In addition, the WG has concerns regarding safety of PRP with regard to the exposure of embryos in the endometrial cavity following PRP injection (and the related growth factors). In addition, no safety evidence exists regarding the potential short- or long-term effects of injection of PRP in the ovarian stroma. In contrast, no adverse effects were reported or expected with microfluidics, however, more research is necessary to prove benefit
Dietmar Spitzer Maximilian Murtinger Maximilian Schuff	20	788-791	The statement of the GPR that: "A Cochrane review showed that IMSI does not improve LBR (….) and clinical pregnancy (…) …" is not is not entirely correct. The statement of the Cochrane review authors' conclusion (Teixeira et al, 2020) was that they are uncertain of the benefit of IMSI over ICSI and that they found very low-quality evidence that IMSI increases clinical pregnancy, which means that they are still very uncertain about any real difference. We think that his makes a subtle but important difference in interpretation. The lack of robust data does not necessarily mean a lack of effect.	The text was adapted.
11. GROWTH FACTOR-SUPPLEMENTED EMBRYO CULTURE MEDIUM				
Verena Nordhoff	20	812	See also Pock et al. 2022; doi: 10.1371/journal.pone.0263793. eCollection 2022	The WG decided to include this study in the text.
Ramos Liliana	21	825	Please add data about the babies born from the culture of embryos with growth factors in medium. I think this might be a very important safety issue	This is already mentioned in the safety paragraph
12. ASSISTED HATCHING				
Bryan Woodward	21	839	Suggest replacing "zona" with "ZP" (twice in this line).	This was adapted as suggested.
Cristina Magli	21	855	The increase in multiples is related to the transfer of more than one embryo, not to the technique itself, unless the result is referred to the implantation rate. I would reformulate the sentence.	The text was adapted.
Xavier Vinals Gonzalez	22	863	This is in line with The National Institute for Clinical Excellence (NICE) guidelines (2013), stating that assisted hatching should not be recommended with the current evidence.	Thank you for your comment, no further action required.
13. GENETIC TESTING/TREATMENT				

Danilo Cimadomo Antonio Capalbo	/	/	In general, we advocate a broader definition of PGT-A efficacy, that should include outcomes such as the reduction of multiple pregnancies, and a more precise definition and presentation of LBR per cycle and per transfer. To our knowledge, up to date, PGTA is the only available approach that involved a universal adoption of a single embryo transfer (SET) policy, also amongst advanced maternal age patients. Especially since SET is a priority in IVF, which has been indeed continuously advocated across the last decades, we think that more emphasis is due to support this as an advantage of PGT-A. Moreover, the presentation of the results of the clinical studies in the Table should be improved. Increasing the LBR per ITT or per egg retrieval is certainly not an expected outcome of PGT-A, which is a diagnostic procedure and not a therapeutical approach to cure aneuploidies.	The WG agrees that (C)LBR is not an ideal outcome measure for PGT-A (a fact which in itself should raise eyebrows about the usefulness of the test) and therefore the alternatives (miscarriage rate and TTP) are now discussed.
Christian S Ottolini Teodora Popa Colin J Davis	/	/	We strongly disagree with the fact that, in evaluating the evidence of PGT-A in regard to safety and efficacy, the authors only included evidence following RCTs, while ignoring the available relevant observational studies. This contrasts with evidence presented for other add-ons where data from observational studies was taken into consideration. We also believe that PGT-A is far more than an embryo selection tool to improve live birth rates. Consideration should be given to assess the safety and accuracy of the test for diagnosing aneuploidy which currently is not included in this document. Lastly and perhaps most importantly, given the drive of most societies in reproductive medicine (including ESHRE) towards elective single embryo transfer (eSET), it would be sensible in our view also to acknowledge the evidence which supports PGT-A as being a robust tool for reducing multiple pregnancies and associated clinical complications for both mother and baby.	Observational studies in other add-ons were only considered when no RCTs were available.
Chi Chiu Wang	/	/	This is not quite relevant to the topic of this review. Main table of included studies is lacking.	A summary table with the recommendations and the quality and strength of the evidence will be published as an annex to the recommendations paper.
Christian S Ottolini Teodora Popa Colin J Davis	3	118	We believe to limit this document to evaluating the efficacy of treatment to live birth rate (LBR) only constitutes a failure to consider properly and fully the merits of PGT-A. There are other outcomes such as miscarriage rate and rate of multiple pregnancy that are increasingly relevant especially for add-ons including PGT-A for which evidence exists to support its use. Our firm view is that the efficacy of treatment in modern IVF should be more focused on how a patient arrives at a live birth, minimising complications, rather than simple live birth outcomes.	(cumulative) LBR was identified as the critical outcome to evaluate the different add-ons discussed in the recommendations paper. In addition, the time-to-pregnancy and miscarriage rate after PGT-A are also discussed in the text.
Elena Kostova	22	869	“not unreasonable assumption” – perhaps phrase differently (ie expected)	A "not unreasonable assumption" was changed to "valid assumption"

Danilo Cimadomo Antonio Capalbo	22	869	“not unreasonable assumption”. We think this should be rephrased as “the reasonable assumption”	A "not unreasonable assumption" was changed to "valid assumption"
Christian S Ottolini Teodora Popa Colin J Davis	22	880	As previously stated (point to lines 118-120 in the General Comments section), the definition of efficacy of an add-on should be broadened to include such matters as positive predictive value to avoid negative outcomes. The accuracy of PGT-A has been demonstrated in a multicentre, prospective blinded non-selection study (2). The study validated the ability of an aneuploid PGT-A diagnosis to predict the failure of a successful delivery. The PGT-A aneuploid diagnosis clinical error rate was 0%. Omission of this important paper demonstrating the high prognostic value of failure to deliver when an aneuploid result was obtained is a significant deficiency in the current document. Although not an RCT and not demonstrating a tangible uplift in LBR, this is irrefutable evidence that PGT can be used to avoid the transfer of an aneuploid embryo, and thus the associated complications, which is an extremely important consideration when treating patients suffering from infertility. A recent review of the available evidence about aneuploid embryo transfer showed consistent findings of embryo lethality (whether blinded or unblinded study) across several PGT-A assays and clinical settings, supporting very high accuracy of embryo deselection in PGT-A (3). Reference: (2) Tiegs AW, Tao X, Zhan Y, Whitehead C, Kim J, Hanson B, et al. A multicenter, prospective, blinded, nonselection study evaluating the predictive value of an aneuploid diagnosis using a targeted next-generation sequencing-based preimplantation genetic testing for aneuploidy assay and impact of biopsy. Fertil Steril. 2021;115(3):627-37. (3) Capalbo, Poli, Jalas, Forman, Treff. American Journal of Human Genetics 2022.	As the reviewer states, this is not an RCT and does not demonstrate a tangible uplift in LBR, and can therefore be considered as a technical issue resolved by the authors of the paper, rather than an improvement to the method or a change in clinical practice that would make a difference to the patients. The WG therefore considers that this paper does not need to be added to the recommendation paper. Similarly, the Capalbo paper points to mosaicism as an important variable in the outcome for the patient; however, as long as these considerations are not translated into improvements in outcomes for patients supported by hard data as provided by RCTs, the WG considers they should not be included in the current document.

Christian S Ottolini Teodora Popa Colin J Davis	22	880	As previously stated (point to lines 118-120 in the General Comments section), the definition of efficacy of an add-on should be broadened to include such matters as reduction in multiple pregnancy. Single-embryo transfer (SET) has been widely advocated as the only effective means to avoid multiple pregnancy in IVF cycles and its associated adverse effects on both mothers and children (4). PGT-A has been used as an effective tool to maintain high pregnancy rates through eSET of screened embryos and therefore avoid multiple pregnancy following multiple-embryo transfer. The authors of this document have in our view incorrectly interpreted Foreman et al, 2013 (5) using it as evidence that PGT-A does not improve LBR. However this RCT demonstrated that transferring a single euploid blastocyst results in ongoing pregnancy rates that are equivalent to transferring two untested blastocysts (5). References: (1) Practice Committee of the American Society for Reproductive M. Multiple pregnancy associated with infertility therapy. Fertil Steril. 2006;86(5 Suppl 1):S106-10. (2) Forman EJ, Hong KH, Ferry KM, Tao X, Taylor D, Levy B, et al. In vitro fertilization with single euploid blastocyst transfer: a randomized controlled trial. Fertil Steril. 2013;100(1):100-7 e1.	The Forman paper did not assess cumulative birth rates which would have made a better measure regarding eSET. Taking into account the different points of criticism that have been made on this paper, the WG does not deem it opportune to go deeper into the pros and cons of this particular report.
Carmen Rubio	22	883	It is mentioned in the text that: “The earliest RCTs showed some beneficial effect, such as sustained implantation rate (Dahdouh et al., 2015), but were heavily criticized for either being on small groups, using the wrong outcome, or serious methodological flaws (Forman et al., 2013, Mastenbroek and Repping, 2014, Scott et al., 2013, Yang et al., 2012b)”. However, the RCT published by Scott et al., 2013 showed a significantly higher sustained implantation rate in the PGT-A group compared to the control group (66.4% vs. 47.9%). Scott, R.T., Jr.; Upham, K.M.; Forman, E.J.; Hong, K.H.; Scott, K.L.; Taylor, D.; Tao, X.; Treff, N.R. Blastocyst biopsy with comprehensive chromosome screening and fresh embryo transfer significantly increases in vitro fertilization implantation and delivery rates: A randomized controlled trial. Fertil. Steril. 2013, 100, 697–703.	The Dahdouh et al systematic review includes the Scott paper, therefore the mention of 'sustained implantation rate' can be considered as referring to Scott et al. Scott et al. is also mentioned in the Table 1.
Elena Kostova	22	885	The “recent” review instead of the “later” review?	This was adapted as suggested by the reviewer

Danilo Cimadomo Antonio Capalbo	22	885	This Cochrane review published in 2020 includes 13 studies. Nevertheless, its relevance is questionable. In fact, 11/13 of those studies were already 7-17 years old when the review was published (only 1 adopted a blastocyst stage biopsy and 0 adopted a CCT technology for genetic testing). Moreover, neither the only 2/13 recent studies (ESTEEM and STAR trial) mirror the current gold standard for PGT-A: (i) Verpoest et al's ESTEEM trial adopted polar body biopsy, which is scarcely used at present in the clinical context (<1%). Still the authors showed very positive outcomes in favor of PGT-A, namely a similar CLBR/ITT with less embryos transferred, less embryos cryopreserved, and less miscarriages (ii) Munnè et al's STAR trial is characterized by a severely flawed design (namely good prognosis patients with at least two blastocysts included, alleged mosaic embryos reported in 5/9 genetic laboratories and not transferred [resulting in 25 patients in the PGT-A group who did not have transferable embryos], poor control on the participating centers in terms of training and expertise). Still, also in this case, better outcomes were reported in women older than 35 (i.e., the women with an indication to PGT-A).	This is more a comment than a question. Both the Verpoest and Munné and the main criticisms as raised by the reviewers are mentioned in the recommendations paper. The WG recognised the shortcomings of the Cornelisse paper that was raised by other reviewers as well; however, this work was carried out according to the state of the art and therefore cannot be ignored.

Carmen Rubio	22	885	There have been several studies showing no improvements with the use of PGT-A. Some of these studies were also heavily criticized for the design and the technical aspects, but these are not mentioned. Only the criticisms of the studies with positive results are commented. Another important aspect is to identify if the results are different for different indications and, also the outcome variables to consider. Regarding the first part, currently there is general agreement that PGT-A can help in AMA patients, improving ongoing pregnancy rates per transfer, decreasing miscarriage rates and time to pregnancy, and these outcome variables are important for patients undergoing IVF treatments. Some more studies related to AMA should be included, RCTs and retrospective. And the benefits of the STAR trial in the subgroup of AMA should be mentioned too. Rubio C, Bellver J, Rodrigo L, Bosch E, Mercader A, Vidal C, De los Santos MJ, Giles J, Labarta E, Domingo J, Crespo J, Remohí J, Pellicer A, Simón C. Preimplantation genetic screening using fluorescence in situ hybridization in patients with repetitive implantation failure and advanced maternal age: two randomized trials. Fertil Steril. 2013 Apr;99(5):1400-7. Rubio C, Bellver J, Rodrigo L, Castillón G, Guillén A, Vidal C, Giles J, Ferrando M, Cabanillas S, Remohí J, Pellicer A, Simón C. In vitro fertilization with preimplantation genetic diagnosis for aneuploidies in advanced maternal age: a randomized, controlled study. Fertil Steril. 2017 May;107(5):1122-1129. Analysis of IVF live birth outcomes with and without preimplantation genetic testing for aneuploidy (PGT-A): UK Human Fertilisation and Embryology Authority data collection 2016–2018. Kathryn D. Sanders, Giuseppe Silvestri, Tony Gordon, Darren K. Griffin. J Assist Reprod Genet. 2021 Dec; 38(12): 3277–3285. Effect of trophectoderm biopsy for PGT-A on live birth rate per embryo in good prognosis patients. Michael S. Awadalla, Ravi Agarwal, Jacqueline R. Ho, Lynda K. McGinnis, Ali Ahmady . Arch Gynecol Obstet. 2022; 306(4): 1321–1327. Published online 2022 Jul 12. doi: 10.1007/s00404-022-06679-x PMCID: PMC9470687 Trends and Outcomes for Preimplantation Genetic Testing in the United States, 2014-2018. Heather S. Hipp, Sara Crawford, Sheree Boulet, James Toner, Amy A. E. Sparks, Jennifer F. Kawwass JAMA. 2022 Apr 5; 327(13): 1288–1290. Published online 2022 Apr 5. doi: 10.1001/jama.2022.1892 PMCID: PMC8984775 Wang L, Wang X, Li M, Liu Y, Ou X, Chen L, Shao X, Quan S, Duan J, He W, Shen H, Sun L, Yu Y, Cram DS, Leigh D, Yao Y. PGT-A: The biology and hidden failures of randomized control trials. Prenat Diagn. 2022 Aug;42(9):1211-1221. In addition, the ESHRE Guidelines for RIF PGT-A suggests that that PGT-A can be considered as an acceptable intervention.	The WG agrees that (C)LBR is not an ideal outcome measure for PGT-A. However, few RCTs included shorter time to pregnancy or miscarriage rate even in their secondary outcomes. The Rubio 2013 paper was excluded on the basis that the test used was FISH, which all agree is not acceptable anymore. A sentence to clarify this has been added to the text. The Rubio 2017 is an unfortunate oversight and is added to the text and table 1. The Sanders and Hipp papers are data mining in respectively HFEA and SART, just like the most recent work of Kucherov et al. which had contradicting conclusions to the previous 2 papers. As these are not RCT, they are not included in the paper.
Cristina Magli	22	887	For a correct information, it should be specified that of the 13 RCTs included, only 2 used 24-CCS, 1 of which was on PBs.	This was added to the tekst

Danilo Cimadomo Antonio Capalbo	22	889	“a large Chinese RCT in younger patients (20 – 37-year-old) also failed to show improvement in live birth rates per cycle”. This is a severe misconception that should be prevented (and not reinforced) by this working group: PGT-A cannot improve the CLBR per cycle. It can only help achieving the same CLBR with less transfers, less miscarriages, and a negligible residual risk of chromosomal syndromes in the newborns. The fact that PGT-A in a "large Chinese RCT" (i) including only good prognosis patients (with no conventional indication to PGT-A) (ii) who produced at least 3 blastocysts and (iii) where alleged mosaic embryos were reported and not transferred, did not reduce the chance of LB per cycle actually is a very positive outcome.	The WG agrees that (C)LBR is not an ideal outcome measure for PGT-A (a fact which in itself should raise eyebrows about the usefulness of the test) and therefore the alternatives (miscarriage rate and TTP) are now discussed. The criticism on the Chinese study was already included in the 'Efficacy' paragraph.
Carmen Rubio	23	897	Table 1 indicates that Forman et al., 2013 found no differences in ongoing pregnancy rate per randomized patient after the first ET. It is important to mention that there weren’t multiple pregnancies in the PGT-A arm, whereas the control arm had an incidence of 53.4%, demonstrating that PGT-A could decrease this complication without compromising success rates. In the same table, it is indicated that Verpoest et al., 2018 showed no differences in the LBR per patient in the group of patients performing PGT-A of PBs compared to controls (24% vs 24%). However, when comparing the results per embryo transferred, the PGT-A group showed double LBR compared to controls (20.1% vs 10.2%). As commented in the revision performed by Viotti et al., 2020, these findings should be mentioned, as they are important for countries that forbid culturing embryos to the blastocyst stage. Viotti M. Preimplantation Genetic Testing for Chromosomal Abnormalities: Aneuploidy, Mosaicism, and Structural Rearrangements. Genes (Basel). 2020 May 29;11(6):602. doi: 10.3390/genes11060602. PMID: 32485954; PMCID: PMC7349251. Also in this table, in the publication from Munne eat al., 2019, the sub-analysis results in the population of AMA should be mentioned.	When analysing RCTs, this working group can only report on the primary and secondary outcome measures set by the authors. The main therapeutic measure against multiple pregnancies is the transfer of only one embryo; transferring more embryos whether tested or untested will always lead to higher multiple pregnancy rates.

Christian S Ottolini Teodora Popa Colin J Davis	23	902	The safety of blastocyst biopsy has been demonstrated in randomised and paired clinical trials (1). After selecting two embryos for transfer, one was randomised to biopsy and the other to control and transferred shortly thereafter. Trophectoderm-biopsied embryos showed sustained implantation rates equivalent to control blastocysts. In contrast, cleavage-stage biopsy was showed to reduce embryonic potential (1). This is one (perhaps the best) example of several in the published literature, demonstrating the safety of the technical aspects of PGT-A which we feel is extremely relevant when evaluating it as an add-on. We feel that omission of this evidence regarding the safety of the technical aspects is a significant oversight and we would request it is addressed. Reference: (1) Scott RT, Jr., Upham KM, Forman EJ, Zhao T, Treff NR. Cleavage-stage biopsy significantly impairs human embryonic implantation potential while blastocyst biopsy does not: a randomized and paired clinical trial. Fertil Steril. 2013;100(3):624-30.	We have included a more recent meta-analysis of the effect of PGT on obstetric and neonatal outcome (Zheng et al., 2021) which we deem to better cover the safety aspect than a single study focusing on implantation and not on longer term effects.
Danilo Cimadomo Antonio Capalbo	23	909	Several more references can be mentioned here that showed no impact of PGT on gestational, perinatal, neonatal, and long-term post-birth follow up data (e.g., Sites et al AJOG 2021 https://doi.org/10.1016/j.ajog.2021.04.235; Natsuaki and Dimler World Journal of Pediatrics 2018 https://doi.org/10.1007/s12519-018-0172-4)	The Sites paper retrospectively analyses SART data and is therefore excluded. Natsuaki and Dimler did not analyse obstetric outcomes such as hypertensive disorders of pregnancy (which is reported in the Zheng paper) but are now included.
Danilo Cimadomo Antonio Capalbo	23	table I	We think that writing "no difference" with respect to Forman et al, 2013 RCT is misleading if you consider that this outcome was achieved by transferring half of the embryos (1 euploid vs 2 untested blastocysts). Also regarding Verpoest et al, 2018 claiming "No difference" is highly misleading for two reasons: (i) similar CLBR per patient is an extremely good outcome and it is in line with the theory upon which PGT-A itself is grounded (i.e., providing the same efficacy but a higher efficiency than conventional IVF), (ii) the relative risk for a LBR per transfer was 1.83 (1.26-2.65) when euploid (33% LBR) rather than untested embryos (18% LBR) were transferred, again an extremely positive outcome. We do not think these outcomes can be ignored here.	The WG agrees that (C)LBR is not an ideal outcome measure for PGT-A (a fact which in itself should raise eyebrows about the usefulness of the test) and therefore the alternatives (miscarriage rate and TTP) are now discussed.
Christian S Ottolini Teodora Popa Colin J Davis	23	table I	Regarding Foreman et al, 2013 (5), it should be noted that the “no difference” in LBR was comparing transfer of a single screened embryo against transfer of two unscreened embryos. It is evident therefore that there is very much a difference. It also demonstrated that the multiple pregnancy rate was significantly lowered in the PGT-A group (as mentioned in point to line 880). Reference: (5) Forman EJ, Hong KH, Ferry KM, Tao X, Taylor D, Levy B, et al. In vitro fertilization with single euploid blastocyst transfer: a randomized controlled trial. Fertil Steril. 2013;100(1):100-7 e1.	The WG agrees that (C)LBR is not an ideal outcome measure for PGT-A (a fact which in itself should raise eyebrows about the usefulness of the test) and therefore the alternatives (miscarriage rate and TTP) are now discussed.

Cristina Magli	24	914	Word missing after “very”.	We did not find an instance of the word 'very' that missed a word after it.
Carmen Rubio	24	921	It is mentioned in the text that: “PGT-A is hypothesized to shorten the time to pregnancy. This outcome has, so far, only been reported in the RCT by Verpoest et al., who found no significant difference in time to pregnancy between the PGT-A and control group (Verpoest, et al., 2018).”. However, other publications show positive conclusions in favor of PGT-A regarding this concept. A RCT conducted by Rubio et al., 2017 confirmed lower time to pregnancy in the PGT-A group in AMA patients (7.7 vs. 14.9 weeks) (Rubio et al., 2017). Neal et al., 2018 described that IVF with PGT-A decreases time in treatment, with a shorter average time from retrieval to embryo transfer resulting in live birth or completion of treatment due to exhaustion of the embryo cohort. Specially in patients with more than two embryos, PGT-A decreased time in treatment by more than three months. Somigliana et al, also did a cos-effectiveness study, identifying the patients that can benefit from PGT-A. Rubio C, Bellver J, Rodrigo L, Castillón G, Guillén A, Vidal C, Giles J, Ferrando M, Cabanillas S, Remohí J, Pellicer A, Simón C. In vitro fertilization with preimplantation genetic diagnosis for aneuploidies in advanced maternal age: a randomized, controlled study. Fertil Steril. 2017 May;107(5):1122-1129. Neal SA, Morin SJ, Franasiak JM, Goodman LR, Juneau CR, Forman EJ, Werner MD, Scott RT Jr. Preimplantation genetic testing for aneuploidy is cost-effective, shortens treatment time, and reduces the risk of failed embryo transfer and clinical miscarriage. Fertil Steril. 2018 Oct;110(5):896-904. 1. Somigliana, E.; Busnelli, A.; Paoni, A.; Vigano, P.; Riccaboni, A.; Rubio, C.; Capalbo, A. Cost-effectiveness of preimplantation genetic testing for aneuploidies. Fertil. Steril. 2019:111: 1169–1176.	The Rubio 2017 reference was mistakingly omitted from this work. The sentence is changed accordingly.

Carmen Rubio	24	924	It is mentioned that “PGT-A is a costly procedure, demanding skilled personnel for the biopsy and genetic analysis, as well as an important investment in genetic analysis instrumentation which is often passed on to the patient (van de Wiel et al., 2020).” Neal et al., 2018 analyzed cost-effectiveness of PGT-A demonstrating overall cost savings for patients with more than one embryo who choose to undergo IVF/PGT-A as opposed to IVF alone (Neal et al., 2018), by reducing healthcare costs, shorten treatment time and reducing the risk of failed embryo transfer and clinical miscarriages. Additionally, a theoretical cost-effectiveness study performed by Somigliana et al. 2019 stated that cost-effectiveness profile of PGT-A improves with female age and number of available blastocysts. Neal SA, Morin SJ, Franasiak JM, Goodman LR, Juneau CR, Forman EJ, Werner MD, Scott RT Jr. Preimplantation genetic testing for aneuploidy is cost-effective, shortens treatment time, and reduces the risk of failed embryo transfer and clinical miscarriage. Fertil Steril. 2018 Oct;110(5):896-904. Somigliana E, Busnelli A, Paffoni A, Vigano P, Riccaboni A, Rubio C, Capalbo A. Cost-effectiveness of preimplantation genetic testing for aneuploidies. Fertil Steril. 2019 Jun;111(6):1169-1176.	Both the Neal and Somigliana studies were cost-effectiveness analyses; moreover Somigliana et al. specifically mention 'we did not include time to pregnancy analyses in our study'. They are added for completeness in the 'Other aspects' paragraph.
Carmen Rubio	24	927	Considering the mentioned studies, the recommendation section shouldn’t state that routine use of PGT-A is not recommended, as it has been demonstrated its benefit in certain indications, as reviewed in Viotti et al. 2020, with the conclusion that in many settings PGT-A has demonstrated its capability to improve likelihood of positive outcome is undeniable and tremendously valuable. And AMA and RIF are clear indications to be considered for recommendation (as in RIF Guidelines). Our suggested recommendation would be: Viotti M. Preimplantation Genetic Testing for Chromosomal Abnormalities: Aneuploidy, Mosaicism, and Structural Rearrangements. Genes (Basel). 2020 May 29;11(6):602. doi: 10.3390/genes11060602. PMID: 32485954; PMCID: PMC7349251.	The WG does not agree with this conclusion, and the focus is now on the proponents of PGT-A to show using hard first class evidence in which patient populations it works.
Sarah Lensen Andy Vail Jack Wilkinson	24	928	The final recommendation for PGT-A states “However, PGT-A may decrease time to pregnancy in specific patient groups”. We could not see any data presented to support this claim in the document. - What is the purpose of this statement if the “specific patient groups” are not named or remain at the imagination of the reader? Would this not be true for any intervention, then? - Note that where this claim is made, it is often based on a basic statistical error, as described here: https://raf.bioscientifica.com/view/journals/raf/2/2/RAF-21-0015.xml	The recommendation was adapted.

Danilo Cimadomo Antonio Capalbo	24	928	"Based on the current evidence showing lack of improvement of live birth rates, or a decrease in miscarriage, routine use of PGT-A is not recommended". Both Dahdouh et al FS 2015 http://dx.doi.org/10.1016/j.fertnstert.2015.08.038 and Chen et al Plos One 2015 DOI:10.1371/journal.pone.0140779 systematic reviews and meta-analyses should be mentioned and discussed for PGT-A. In fact, both reported consistently higher implantation rates per ET and lower miscarriage rates when euploid (diagnosed via CCT with no alleged mosaicism reports) versus untested embryos are transferred. Moreover, some observational studies in the context of AMA patients cannot be disregarded (e.g., Ubaldi et al HR 2015 DOI: 10.1093/humrep/dev159; Sacchi et al JARG 2019 doi: 10.1007/s10815-019-01609-4; Haviland et al HR 2020 doi: 10.1093/humrep/deaa161). In fact, these authors reported similar CLBR per cycle with higher LBR per ET, less miscarriages and less embryos transferred when PGT-A was adopted. Indeed PGT-A finds its main application in this category of poor prognosis patients subject to high risks of aneuploidies. In this regard, we also think that "routine use of PGT-A" is indeed an ambiguous wording. What do you mean by "routine"? What about solid indications to PGT-A such advanced maternal age and recurrent pregnancy loss? The authors should be clearer here. Also, we question how the authors included only the evidence following RCTs, while ignoring the available relevant observational studies. This contrasts with evidence presented for other add-ons where data from observational studies was indeed included and used to deliver recommendations. At last, we think the authors should mention the data comprehensively summarized by Capalbo et al recently in AJHG 2022 and showing that full chromosome aneuploidies reported at the blastocyst stage are predictive of >98% lethality rate if the embryos are transferred in the context of non-selection studies (DOI: 10.1016/j.ajhg.2022.07.009). In particular, this last study clearly highlights that deselecting embryos affected from uniform aneuploidies is a highly effective strategy, even when measured across different PGT-A assays and clinical settings (= good reproducibility).	Dahdouh et al. is discussed in the manuscript. Furthermore, only RCTs were considered for PGT-A. There are no RCTs on AMA or RIF to unequivocally show benefit, only posthoc analyses. The Capalbo paper in AJHG is a research paper and while showing lethality of aneuploid embryos, it does not place this into a clinical setting with all the added variables this entails.
Elena Kostova	24	929	It is not clear to which "specific patient groups" the statement refers. Referring to Verpoest at al 2019 (lines 922-923) authors say there were no significant difference in time to pregnancy between the PGT-A and control group.	The recommendation was adapted.
Tarek El-Toukhy	24	929	The recommendation that "PGT-A may decrease time to pregnancy in specific patient group" is unjustified by the available evidence and the only study referenced in the guideline document with regard to time to pregnancy (Verpoest at al, 2018) showed no difference in time to pregnancy between the PGT-A and control groups. Therefore, this section of the recommendation should be removed to avoid being used as a justification for offering an unproven, expensive, invasive and potentially detrimental add-on treatment to vulnerable IVF patients desperate to conceive promptly.	The recommendation was adapted.
Ahmed Fawzy Galal	24	930	I think better to specify the specific group to have a strong recommendation	The recommendation was adapted.

Arianna D'Angelo	24	942	recommendation is missing ; I can see it is merged in the section below but for consistency throughout the paper after each add on there should be a recommendation. This suggestion also applies to more adds on listed after. For some of which there is a recommendation and for others there is a merged recommendation. This can be somehow confusing.	The recommendations for niPGT and mtDNA quantification have been split.
Danilo Cimadomo Antonio Capalbo	24	942	Although we agree that "both methods are still considered to be in development and not suitable for clinical application", we also think that the statement "It can be assumed that niPGT-A represents even lower risk for the ensuing pregnancy and baby" should consider the risk for possible false negative errors, imputable for instance to contamination, low DNA yield or quality, and their consequences. Similarly, the working group should strongly advise against discarding embryos reported "aneuploid" based on niPGT-A, since this strategy is subject to high False Positive call rates.	The sentence has been changed to clarify the distinction between diagnostic accuracy and safety of biopsy.
Sarah Lensen Andy Vail Jack Wilkinson	24	942	It is not clear what aspects were considered in terms of 'Safety' and how these factored into the recommendations. Safety of ni-PGT-A "It can be assumed that niPGT-A represents even lower risk for the ensuing pregnancy and baby." It is not clear what the comparator is – compared to standard PGT-A or compared to IVF without PGT-A? If ni-PGT-A doesn't in fact work at all (given this is yet to be established), is there not potential for the test to result in more babies born with down syndrome etc compared to PGT-A? This seems to be the only example where the authors have decided to make an assumption about safety rather than rely on data.	The sentence has been adapted to clarify.
Cristina Magli	24	942	A Recommendation paragraph to be included.	The recommendations for niPGT and mtDNA quantification have been split.
Cristina Magli	25	957	To be consistent, it should be added "Therefore, the clinical application is not recommended".	This was added to the text.
Elena Kostova	25	/	If published before this document is finalized, you should add the results of Kieslinger at al (SelecTIMO study) currently under peer review.	Papers published up to August 2022 are included. At the time of stakeholder review, the study mentioned is still not published.
14. TIME-LAPSE IMAGING				
Ramos Liliana	25	958	Time Lapse imaging: in this section add the data from the SELECTIMO trial (Trial NL5314 (NTR5423) study presented at ESHRE in Milan	According to the ESHRE manual for guideline development, conference abstracts are not eligable to be included in the body of evidence

Tine Qvistgaard Kajhøj	25	963	Suggest replacing ”and using various morphokinetic parameters such as the timing of cell divisions and intervals between cell cycles, may improve embryo selection presumed to increase LBR and time to pregnancy rate by selecting and freezing the embryos with the highest implantation potential” With something like: “and improved embryo selection, based on developmental features identified through imaging, may increase LBR, cumulative live birth rate and time to pregnancy by selecting and freezing the embryos with the highest implantation potential. Embryo selection can be based on a range of standardized morphokinetic parameters as well as dynamic morphology including observation of multinucleation, and fragmentation which may be missed or incorrectly identified without time-lapse imaging. Time-lapse also ensures correct evaluation of pronuclear status which may be missed by standard evaluation. According to a recent study, up to 11% of embryos would have been incorrectly labelled as unfertilized using the ESHRE Istanbul recommended PN check time range, resulting in potential erroneous discarding of viable embryos [1]. Recently, new methods for embryo selection have been developed based on artificial intelligence analyzing the whole time-lapse sequence [2]. One study has retrospectively found a correlation between a deep learning based model and LBR and miscarriage [3]. 1. Barrie, A., et al., Optimisation of the timing of fertilisation assessment for oocytes cultured in standard incubation: lessons learnt from time-lapse imaging of 78 348 embryos. Hum Reprod, 2021. 36(11): p. 2840-2847. 2. Tran, D., et al., Deep learning as a predictive tool for fetal heart pregnancy following time-lapse incubation and blastocyst transfer. Hum Reprod, 2019. 34(6): p. 1011-1018. 3. Ueno, S., et al., Correlation between an annotation-free embryo scoring system based on deep learning and live birth/neonatal outcomes after single vitrified-warmed blastocyst transfer: a single-centre, large-cohort retrospective study. J Assist Reprod Genet, 2022. 39(9): p. 2089-2099.	The WG does not agree with the reviewer's comment. Phrases such as "improved embryo selection", and "highest implantation potential" are not supported by current evidence. The text will remain as it stands.
Tine Qvistgaard Kajhøj	25	968	Suggest to include that there are conflicting data on how generalizable algorithms are. Other validations have shown a general morphokinetic model to correlate with LBR [4].” 4. Bori, L., et al., The higher the score, the better the clinical outcome: retrospective evaluation of automatic embryo grading as a support tool for embryo selection in IVF laboratories. Hum Reprod, 2022. 37(6): p. 1148-1160.	The WG does not think it is necessary to go into detail on algorithms for TLI in this recommendations paper. The reader is referred to the ESHRE recommendations paper on the use of time-lapse technology.
Tine Qvistgaard Kajhøj	25	971	Suggest to mention QC in this sentence “…laboratory workflows (ESHRE Working group on Time-lapse technology et al., 2020) and may also be useful as a QC indicator [5]” 5. Wolff, H.S., et al., Advances in quality control: mouse embryo morphokinetics are sensitive markers of in vitro stress. Hum Reprod, 2013.	The sentence was adapted. The suggested reference is cited in the ESHRE recommendations paper on the use of time-lapse technology.

Tine Qvistgaard Kajhøj	25	975-985	For the mentioned Cochrane review, concerns questioning the conclusions of the report and placed to the authors should be considered (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011320.pub4/epdf/full , specifically pg 61-66). Several publications show a positive effect of including TL based algorithms during embryo evaluation. The meta-analysis by Pribenszky et al 2018 which shows a positive effect of applying time-lapse and time-lapse based selection shown as reduced pregnancy loss, higher ongoing pregnancy and higher live birth rate [6] should be included. 6. Pribenszky, C., A.M. Nilselid, and M. Montag, Time-lapse culture with morphokinetic embryo selection improves pregnancy and live birth chances and reduces early pregnancy loss: a meta-analysis. Reprod Biomed Online, 2017. 35(5): p. 511-520.	The lastest Cochrane review and meta-analysis is more recent (2019) than the Pribenszky meta-analysis (2018). Therefore there is no need to include the Pribenszky meta-analysis.
Tine Qvistgaard Kajhøj	25	985	Suggest to replace: ”based on the quality of evidence,” With: “based on the quality of evidence of the included studies”.	This was adapted as suggested.
Tine Qvistgaard Kajhøj	25	985	Suggest to add: “It should be noted that there are various algorithms from different suppliers and there is a difference in how these are clinically validated and their clinical performance.”	The reader is referred to the ESHRE recommendations paper on the use of time-lapse technology earlier in this chapter for more information on algorithms for embryo selection.
Tine Qvistgaard Kajhøj	25	987	Suggest to broaden the safety evidence by: 1) adding “benchtop” the sentence “…safe as embryo culture in conventional and benchtop incubators…” 2) supporting the statement of safety with more evidence. Suggestions: [7-10] 7. Reignier, A., et al., Time-lapse technology improves total cumulative live birth rate and shortens time to live birth as compared to conventional incubation system in couples undergoing ICSI. J Assist Reprod Genet, 2021. 38(4): p. 917-923. 8. Sciorio, R., J.K. Thong, and S.J. Pickering, Comparison of the development of human embryos cultured in either an EmbryoScope or benchtop incubator. J Assist Reprod Genet, 2018. 35(3): p. 515-522. 9. Cimadomo, D., et al., Continuous embryo culture elicits higher blastulation but similar cumulative delivery rates than sequential: a large prospective study. J Assist Reprod Genet, 2018. 35(7): p. 1329-1338. 10. Setti, A.S., et al., Improved embryonic development and utilization rates with EmbryoScope: a within-subject comparison versus a benchtop incubator. Zygote, 2022. 30(5): p. 633-637.	Benchtop was added to the sensence. The WG does not think it is necessary to cite more evidence.

Bryan Woodward	25	990	Suggest removing “In the UK..” as, whilst this is true, many clinic across the globe do the same thing!	This was adapted as suggested. However, the quoted study only looked at UK websites.
Cristina Magli	25	990	I would delete “In the UK”.	This was adapted as suggested. However, the quoted study only looked at UK websites.
Bryan Woodward	26	995	Suggest this sentence could be reworded. TLI is not an incubator. There are incubators that incorporate in-built TLI, e.g. EmbryoScope; but there are also TLI devices that are placed within standard box incubators.	The sentence was adapted.
Tine Qvistgaard Kajhøj	26	995	Suggest to change: “Time-lapse imaging has been shown to be a convenient and effective incubator which allows a continuous view of embryo development.” To: “Time-lapse systems have been shown to be convenient and effective incubators which allows a continuous view of embryo development.” The rationale for this suggestion is to reflect that effective incubation and continuous viewing is obtained by the full system.	The sentence was adapted.

Tine Qvistgaard Kajhøj	26	996	Suggest to add “However there are sufficient studies, both retrospective analysis and RCTs to show that some TL devices improve embryo development and quality, which may lead to improved cumulative pregnancy and live birth [8, 11-14]. In retrospective studies, proportion of good quality and useable embryos at both cleavage and blastocysts stage has been shown. 2 RCTs and a sibling embryo study also confirm these findings. Alhelou et al showed the number of 8+ cells on day 3 and number of blastocyst was significantly higher in a time-lapse system compared to a standard benchtop incubator. Implantation rate was also significantly higher in the time-lapse system [13]. In an RCT by Barberet et al. top quality embryos on day 2, cryopreserved embryos on day 5/6 and total percentage of viable embryos was higher in a time-lapse system than those cultured in a bench top incubator. Although there was no significant differences in clinical outcomes there was a clear higher trend for clinical pregnancy, implantation and ongoing pregnancy per woman and per transfer. It should be noted this did not reach statistical significance and was powered to show a 48% relative improvement. Time-lapse information was not used to select embryos [12]. A recent sibling study showed that there were more blastocysts and cryopreservable blastocysts in a time-lapse system versus a benchtop incubator [14]. Interestingly, the embryos cultured in the time-lapse system had a significantly higher utilization of 12 amino acids than embryos cultured in a standard incubator. It is clear that both retrospective and prospective studies show a higher number and quality of embryos which may improve cumulative pregnancy rates. Reignier et al, showed that patients having all cycles in a time-lapse system versus patients solely using standard culture and evaluation, had a significantly higher total cumulative live birth rate and shorter median time to live birth [7]. This finding supports potential for improved cumulative live birth using a time-lapse system. 11. Ueno, S., et al., Closed embryo culture system improved embryological and clinical outcome for single vitrified-warmed blastocyst transfer: A single-center large cohort study. Reprod Biol, 2019. 19(2): p. 139-144. 12. Barberet, J., et al., Randomized controlled trial comparing embryo culture in two incubator systems: G185 K-System versus EmbryoScope. Fertil Steril, 2018. 109(2): p. 302-309.e1. 13. Alhelou, Y., N.A. Mat Adenan, and J. Ali, Embryo culture conditions are significantly improved during uninterrupted incubation: A randomized controlled trial. Reprod Biol, 2018. 18(1): p. 40-45. 14. Kermack, A.J., et al., Incubator type affects human blastocyst formation and embryo metabolism: a randomized controlled trial. Human Reproduction, 2022.	The most recent Cochrane review concluded that there is insufficient good-quality evidence that TLI improves BR, ongoing PR, reduces miscarriage or stillbirth. The WG sees no need to change the recommendation based on the suggested references.
Cristina Magli	26	997	I would add “so, it cannot be promoted as an advantage for the patient”.	The sentence was adapted.
Ahmed Fawzy Galal	26	997	Adding especially in respect to cost effectiveness rationale	The comment is unclear, unfortunately the WG cannot address it.

15. PLATELET RICH PLASMA (PRP)				
Rukhsana Karim	26	999	1- Molina A, Sánchez J, Sánchez W, Vielma V. Platelet-rich plasma as an adjuvant in the endometrial preparation of patients with refractory endometrium. JBRA Assist Reprod. 2018 Mar 1;22(1):42-48. doi: 10.5935/1518-0557.20180009. PMID: 29303234; PMCID: PMC5844658…….. Endometrial thicknesses >7mm was reported with the first use; and in all cases, endometrial thicknesses >9mm were evident after the second administration. The entire study group qualified for Embryo Transfer at the blastocyst stage. We had 73.7% of positive pregnancy tests, of which 26.3% yielded live births; 26.3% ongoing pregnancies; 10.5% biochemical pregnancies; 5.3% anembryonic pregnancies and 5.3% had fetal death (16 weeks) 2- Maleki-Hajiagha A, Razavi M, Rouholamin S, Rezaeinejad M, Maroufizadeh S, Sepidarkish M. Intrauterine infusion of autologous platelet-rich plasma in women undergoing assisted reproduction: A systematic review and meta-analysis. J Reprod Immunol. 2020 Feb;137:103078. doi: 10.1016/j.jri.2019.103078. Epub 2019 Dec 31. PMID: 32006776…… Meta-analysis using a random-effects model was performed to calculate the pooled estimates. Seven studies involving 625 patients (311 cases and 314 controls) were included. The probability of chemical pregnancy (n = 3, risk ratio (RR): 1.79, 95 % confidence intervals (CI): 1.29, 2.50; P < 0.001, I2 = 0 %), clinical pregnancy (n = 7, RR: 1.79, 95 % CI: 1.37, 2.32; P < 0.001, I2 = 16 %), and implantation rate (n = 3, RR: 1.97, 95 % CI: 1.40, 2.79; P < 0.001, I2 = 0 %) was significantly higher in women who received PRP compared with control. There was no difference between women who received PRP compared with control group regarding miscarriage (RR: 0.72, 95 % CI: 0.27, 1.93; P = 0.51, I2 = 0 %). Following the intervention, endometrial thickness increased in women who received PRP compared to control group (SMD: 1.79, 95 % CI: 1.13, 2.44; P < 0.001, I2 = 64 %). The findings of this systematic review suggest that PRP is an alternative treatment strategy in patients with thin endometrium and recurrent implantation failure (RIF). 3- Pourmoghadam Z, Abdolmohammadi-Vahid S, Pashazadeh F, Aghebati-Maleki L, Ansari F, Yousefi M. Efficacy of intrauterine administration of autologous peripheral blood mononuclear cells on the pregnancy outcomes in patients with recurrent implantation failure: A systematic review and meta-analysis. J Reprod Immunol. 2020 Feb;137:103077. doi: 10.1016/j.jri.2019.103077. Epub 2019 Dec 24. PMID: 31893538……five studies being included (two RCTs and three quasi-experimental studies). Finally, all of these article extracted data were pooled in a statistical meta-analysis. Findings demonstrated that implantation, pregnancy and live birth rate were statistically increased and the miscarriage rate was significantly decreased in the PBMC-treated group than that non-treated group.	We thank the reviewer for the additional information. Whereas there are several available studies in favour of PRP, the limitations of the studies had also been mentioned. The scope of the guideline process is to present all the data critically appraising not only the results but also the quality and the methodological design of the studies.

E. Scott Sills	26	1000	the narrative includes a statement which seems to frame the present state of clinical PRP use as limited to orthopedics (see line 1000). Not only is this misleading, it is not even remotely correct. Any 'ovarian rejuvenation' small series or case report informs how PRP technology has been successfully deployed in dermatology, dentistry/oral surgery, wound management, burn care, cosmetic surgery, and numerous other domains. It is therefore puzzling why the field of reproductive medicine is somehow portrayed as just the second application for PRP. Informed readers are at risk to dismiss all that follows, given ESHRE's apparent incomplete grasp of the full PRP story. This would be both unfortunate and unnecessary. While the document later acknowledges ".. a possible overrepresentation of one research group in the data .." (line 1020) this qualifier again undercuts the robustness of the review instead of cautioning the true state of available data. For example, our capture of global ovarian PRP published work agreed last year that this is an area of accelerating study. But many international facilities are participating in the work and no particular center is "overrepresented" in research activity. The lack of RCT data has been (and should continue to be) given as a reason to question the efficacy of autologous intraovarian PRP. Line 1049-1050 wisely concludes with solid advice from ESHRE concerning how this intervention is not yet ready for general use. I endorse that conclusion unreservedly. My brief note here is only offered to identify possible improvements to support that conclusion more properly.	The words related with orthopaedics have been omitted and the recommendation was adapted to its utilization under strict research criteria.
Aboubakr Mohamed Elnashar			Available data are promising only for intrauterine not intraovarian and only for recurrent implantation failure due to thin endometrium not attributes to other factors. Please add	Yes promising, but has not been supported with a RCT yet.
Cristina Magli			As the invasivity of two procedures is different, I would make two distinct recommendations - as it was done for intra-uterine, intra-vaginal devices.	The recommendation was split up as suggested by the reviewer

Sarah Lensen Andy Vail Jack Wilkinson			For PRP, despite multiple (low quality) RCTs suggesting benefit the authors recommend against PRP. Yet for microfluidics, the authors state it "may increase the LBR" based on a single RCT of 128 patients. This trial utilised a commercial test (Fertile Chip) and it's not clear whether the trial was funded by the Chip company. In both cases there is no real safety data. These recommendations therefore appear inconsistent.	For PRP there is significant heterogeneity in application of the method and concentration of the platelets. In addition, the WG has concerns regarding safety of PRP with regard to the exposure of embryos in the endometrial cavity following PRP injection (and the related growth factors). In addition, no safety evidence exists regarding the potential short- or long-term effects of injection of PRP in the ovarian stroma. In contrast, no adverse effects were reported or expected with microfluidics, however, more research is necessary to prove benefit.
16. DUOSTIM				
Carlos Calhaz-Jorge	27	/	About Duostim and Adjuncts during ovarian stimulation. Of course, it's more than correct that the paper refers to the previous Guideline on ovarian stimulation. However, no reference about the many publications after November 2018 (the deadline for the survey of the literature that supported the above Guideline). No relevant information in the last 3 years. Even so, maybe a comment on that could be welcome.	The Ovarian Stimulation guideline is due to be updated, for consistency, the reader is referred to this guideline, which contains the most up-to-date information.
Danilo Cimadomo Antonio Capalbo	27	/	Although DuoStim has been reported safe across several reports in the literature (doi: 10.1080/03009734.2020.1734694), and especially in Vaiarelli et al, HR, 2020 (doi: 10.1093/humrep/deaa203), and a recent RCT showed that it is as effective as double follicular phase stimulation while halving the time needed to obtain at least one euploid blastocyst to transfer (doi:https://doi.org/10.1016/j.rbmo.2022.11.012), we personally think it is off topic to discuss its application in an ESHRE GPR about add-ons. DuoStim simply is an ovarian stimulation strategy that finds application in a population of very poor prognosis patients (AMA and/or POR) that may benefit from oocyte-embryo accumulation policies (or multiple attempts in general) especially since they are highly subject to treatment discontinuation after a failed attempt. In this manuscript a paragraph about "multiple attempts" or "oocyte-embryo accumulation" policies is missing as putative add-ons, therefore we think that DuoStim should not be mentioned as well.	The Ovarian Stimulation guideline is due to be updated, for consistency, the reader is referred to this guideline, which contains the most up-to-date information.
18.INTRAVAGINAL AND INTRAUTERINE CULTURE DEVICE				
Bryan Woodward	28	1106	Isn't there a risk that the embryos could be lost / not retrieved from IVCDs/IUCDs?	There are no published reports of this.

Carlos Calhaz-Jorge	29	1116	The proposed recommendation text seems too much positive considering the absence of robust information. I suggest: "Considering the poor quality of the information published, there is no evidence that intravaginal culture devices can substitute standard IVF with regards to clinical outcomes. It could be…"	The sentence was adapted.
Sarah Lensen Andy Vail Jack Wilkinson	29	1117	It is stated that intravaginal culture device "could be used for its expected psychological benefits." Have these benefits been proven? Could this same argument not be used for any other add-on in which the patient really wants to try it and claims a psychological benefit for this reason?	The line about psychological benefits was deleted from the text.
Ainsley Newson Siun Gallagher Wendy Lipworth	29	1118	Regarding Intra vaginal and intra uterine culture, we note the recommendations focus on "expected psychological benefits." Such benefits are not defined, nor critically interrogated. The place that expected psychological benefits should have in the add-on landscape should be reflected upon, not least because it is likely to be offered as a justification for providing other non-harmful but non-efficacious add-ons. Further, "expected" psychological benefits seems insufficient to justify this recommendation. Further ethical and empirical work is needed (e.g. live birth rate impact, patient acceptability), is required.	The line about psychological benefits was deleted from the text.
Carlos Calhaz-Jorge	29	1127	The proposed recommendation text seems too much positive considering the absence of robust information.	The sentence was adapted.
19. ADDITIONS TO TRANSFER MEDIA				
Mark Larman	29	1143	It should be noted that unlike the other macromolecules mentioned, hyaluronan has been shown to increase in the uterus at the time of implantation in humans (Salamonsen et al., 2001). It also acts as a specific linking molecule between a cell surface receptor (CD44) present on human embryos (Campbell et al., 1995 and Ruane et al., 2020) and stromal cells of the endometrium (Yaegashi et al., 1995). Campbell et al., (1995) CD44 is expressed throughout pre-implantation human embryo development. HR 10 p425. Ruane et al., (2020) The effects of hyaluronate-containing medium on human embryo attachment to endometrial epithelial cells in vitro. HR Open hoz033. Salamonsen et al., (2001) Distribution of hyaluronan in human endometrium across the menstrual cycle. Implications for implantation and menstruation. Cell Tissue Res 306 p335. Yaegashi et al., (1995). Menstrual cycle dependent expression of CD44 in normal human endometrium. Hum Pathol 26 p862.	A sentence was added to the text.
Bryan Woodward	29	1144	isn't the time duration of exposure to HU-enriched media important? Whilst you state "up to 4 hours", some labs strictly expose for just 10 mins, as anything longer reduces success rates (I've only seen this from conference abstracts, rather than papers). It could be worth adding the range to this sentence.	The sentence was adapted.

Zuzana Holubcová	29	1148	there is no evidence of an improved IVF outcome Nevertheless, the recommendation reads it „seems to increase live birth/clinical pregnancy rates“ This notion leaves the impression that there is a positive effect of this procedure. That is the absolute opposite of what your research of literature showed (no clear benefit)!	The Cochrane review including 26 RCTs did show an improvement in live birth rate. However, regarding FET transfers no benefit was shown. Added this to the recommendation
Wellington Martins	29	1150	It is currently suggesting a benefit of hyaluronic acid-enriched transfer medium based on the last published Cochrane review. However, there is a very well performed RCT (Yung et al. 2021) that has shown absolutely no effect of the intervention: Clinical pregnancy = 93/275 (33.8%) vs. 93/275 (33;8%) Live birth = 70/275(25.5%) vs. 71/275 (25.8%) Considering that: - It is an expensive add-on - There is a very high risk of commercial bias in small studies - Any potential benefit should be very small, considering the recently published RCT I suggest authors reconsidering their recommendations regarding this add-on.	This study only concerns FETs, and these results are already mentioned in the text. Our recommendation is only for fresh transfers, now clarified in the recommendation.
Mark Larman	29	1152	Hyaluronan is a macromolecule that can vary in chain length from a few thousand to several million Daltons. EmbryoGlue contains 0.5mg/ml of a particular range of hyaluronan chain lengths. As the Cochrane studies have utilized EmbryoGlue it should be stated that other hyaluronan containing medium might not have the same efficacy. Indeed, evidence for physical difference (viscosity) between embryo transfer media was presented by Reed and Said 2019. Thus, without the equivalent level of clinical testing the efficacy of other hyaluronan transfer media remains uncertain. Perhaps this should be made aware to readers on line 1183. Reed and Said (2019) Estimation of embryo transfer media viscosity and considerations of its effect on media and uterine fluid interactions. RBM Online 39 p931.	The WG considered this outside the scope of this recommendations paper.
Mark Larman	30	1157	To provide some context to actual clinical relevance the number needed to treat (NNT) of 14 could be stated.	This was added to the text.
Mark Larman	30	1158	The Instruction for Use for EmbryoGlue states that embryos should be incubated in the medium for a minimum of 10 minutes. A recent cohort study with more than 3000 transfers (Adeniyi et al., 2021) did not find a difference between “short” (10-30mins) and “long” (2-4hrs) exposure times. When the data was combined and compared to transfers with a low HA medium there were significantly higher clinical pregnancy and live birth rates with the high HA transfer medium, which is further supporting evidence for using EmbryoGlue. Adeniyi et al., (2021) Clinical efficacy of hyaluronate-containing embryo transfer medium in IVF/ICSI treatment cycles: a cohort study. HR Open hoab004.	Cohort studies were only included when there was no RCT addressing the population of interest.

Mark Larman	30	1163	An increase in multiple pregnancy rates following the transfer of more than one embryo supports high concentrations of HA increasing clinical pregnancy rates.	Thank you for this information. No adaptation of the text necessary.
Sarah Lensen Andy Vail Jack Wilkinson	30	1185	"HA addition to transfer media is recommended to be performed only within a single embryo transfer policy program" – the use of EmbryoGlue only in the case of single ET does not appear to be supported by the evidence. The evidence suggests that EmbryoGlue increases multiple pregnancy rates. In the presence of multiple embryo transfer, this is likely to result from any intervention that increases the probability of implantation. It therefore doesn't make sense to recommend against EmbryoGlue in the case of multiple transfer just because the intervention is effective.	The multiple pregnancy rate was found to be increased with the use of high concentration of HA in the transfer media. This was attributed to the combination of transferring multiple embryos and the use of high concentration HA. Therefore, to reduce the multiple pregnancy rate, it is advised to use HA with single embryo transfer.
20. ENDOMETRIAL SCRATCHING				
Carlos Calhaz-Jorge	31	1228	"…The combined result showed that that endometrial…"	This was corrected in the text.
Ahmed Fawzy Galal	32	1235	I think to avoid any confusion we may close the sentence at can not be recommended	The WG considered your suggestion, but would prefer to keep the recommendation in it's current form.
21. FLUSHING OF THE UTERUS				
Carlos Calhaz-Jorge	34	1326	The sentence starts "Three reviews and meta-analyses…" but at the end of it we can find four references. Maybe to remove the last one (Rocha et al) because it's the subject of the following paragraph.	This was corrected in the text.
Sarah Lensen Andy Vail Jack Wilkinson	34	1337	Typo: intrauterine infusion of G-SCF	This was corrected in the text.
Enver Kerem Dirican	32	1260 - 1316	intrauterine hCG administration section seems to be contradictory with GPR on RIF page 751-768	The recommendation was amended in the Recommendations paper on RIF.
22. STEM CELL MOBILISATION				
Arianna D'Angelo	36	1432	explain both acronyms in full	This was corrected in the text.
Carlos Calhaz-Jorge	36	1434	Maybe better to explain the meaning of "HSCs". Not included in the list of abbreviations	This was corrected in the text.
23. STEROIDS				

Sophie Petropoulos	38	/	We have recently published a manuscript with Wolf Reik and Nicolas Rivron where human embryos were exposed to glucocorticoids. This is the first study to examine the impact of adjuvants/additives on the molecular biology of human embryos and I believe would be useful to incorporate into the guidelines either under the use of glucocorticoid or in general as a suggested benchmarking approach to take for assessing the safety of these treatments, particularly when considering the field of Developmental Origins of Health and Disease. Using a single-cell multi-omics approach (transcriptome, small ncRNAs and methylome), our study provides novel and exciting findings pertaining to human preimplantation development. Following exposure to glucocorticoids (GCs), as occurring with maternal stress or the use of adjuvant therapies associated with Artificial Reproductive Technologies (ART) and infertility treatment, our data suggests that the embryos preciously mature. We have determined that the trophectoderm (TE) lineage differentiates resulting in a more refined segregation between the mural and polar lineages around the time of implantation. Further, the polar lineage begins to express markers of extravillous trophoblast cells, which more closely resembles the TE after implantation. Finally, GCs have the ability to achieve X-chromosome inactivation (XCI), which is in contrast to the dual-dosage X-chromosome compensation normally observed during this time, providing novel insight into the regulation of XCI. Our data also suggest that we may be unintentionally programming the embryo toward the development of metabolic disease/disorders later in life and that the transcriptional changes observed are epigenetically mediated (DNA methylation and miRNAs). This study serves as a proof of principle that the human preimplantation embryo is susceptible to molecular reprogramming. As a scientific community we need to be more transparent with both the effectiveness and the possible consequences associated with the use of adjuvants and additives used in ART and the treatment of infertility. I hope that this study will open a larger conversation around this in infertility. We believe our paper will reach a broad scientific community as many of the data generated and insights provided can be utilized in the fields of Developmental Biology, Reproductive Biology, Stem Cell Biology and Artificial Reproduction and Infertility.	Thank you for the suggestion. At this stage, this topic cannot be added to the current recommendations paper. However, we will keep it in mind for the update or the extension of the paper.
24. ELECTIVE FREEZE-ALL				

Forest Garner	39	1527	The draft text will fall flat in the USA, where freeze-all is not some “add-on”, but instead is now the default treatment strategy for all patients at most centers. This is due, in part, to greater success rates with that strategy in the USA. Like the two meta-analyses cited in comparing fresh vs freeze-all, the individual RCTs vary considerably in their conclusions and risk ratios. This reflects what is obvious: the risk ratio is protocol-dependent, there is considerable variation in protocols, and therefore no global truth. The meta-analyses attempt to estimate some global averages that do not apply at the clinic level. Similarly, the average human has one ovary and one testicle, but this average applies to nobody. The text as drafted can only further the divide in practice norms. A more unifying approach would be to recommend that each clinic decide based on the clinic’s own success rates with fresh and freeze-all strategies, and furthermore that centers with decidedly low success rates should modernize their methods. Over the last decade, there has been no valid reason to average less than 50% live birth per transfer in patients <35 with single thawed blastocyst transfer, without the use of PGT-A. RCTs that fall short of this norm are not generalizable to US practice and may be dismissed. Making the recommendation based on local clinic success rates would make the text much more globally applicable. This may seem to fly in the face of evidence-based medicine, but until RCTs using our current protocols exist, and with similar success rates, there is no published evidence relevant to our practices. The freeze-all strategy and thawed embryo transfer protocols are not nearly uniform internationally and are evolving rapidly. Several options have yet to be tried in any RCT comparing fresh vs freeze-all RCTs, and with these in mind, it seems most RCTs unnecessarily constrained their freeze-all arms. The freeze-all strategy is compatible with several methods that would ruin a fresh transfer strategy. These include random-start stimulation (reducing time to pregnancy), prolonged stimulation to obtain more eggs/embryos (potentially increasing success rates in some patient populations), GnRH-agonist trigger in high responders (reducing OHSS risk), and progestins for hypothalamic down-regulation during stimulation (reducing cost and improving LH response to agonist trigger). Other protocol variations exist, such as luteal support, where recent RCTs have shown some common practices to be greatly inferior. As success rates with thawed embryo transfers increase rapidly, reflecting rapid protocol evolution, the published RCTs become mere fossils documenting comparisons of extinct protocols.	PGTa should not be included in this section as this is regarding freeze-all and further no RCT's so far have shown the benefit of PGTa regarding pregnancy and live birth rates. We cannot write a guideline according to current practices in the US. The ESHRE guideline is to the best of our knowledge based on the best current evidence. Freeze-all is an add on procedure with added costs for the patients if not meant to avoid OHSS or other medical reasons for postponing i.e. PGTm/SR, endometrial pathology, egg donation.
Arianna D'Angelo	39	1529	please add reference D'Angelo A and Amso NN cochrane review on elective embryo freezing for prevention of OHSS	The requested reference is a Cochrane review from 2007. The Cochrane review has been updated in 2021 by Zaat et al. and the updated version is included in the guideline. Thus, we have not included the reference by D’Angelo et al. from 2007.

Christos Venetis Efstratios Kolibianakis	39	1529	The authors state: "For the aim of this paper, studies evaluating freeze-all in the context of OHSS prevention were not considered." It has been shown that in expected normal responders although the probability of live birth comparing the 1st frozen embryo transfer with the fresh transfer is not significantly different, the probability of severe OHSS is significantly lower when the freeze all strategy is used. Thus, to accept that a thorough review of the evidence is possible by not considering studies on freeze all in the context of OHSS prevention is highly problematic.	The WG considers it correct not to include OHSS as an outcome in the guideline as we fully state that freeze-all is a preventive strategy to avoid OHSS in risk patients and therefore not considered an add-on in these cases. Further on it has also been shown in Stormlund et al., 2020 that in normo-responders OHSS rates are similar after freeze-all and fresh embryo transfer if a segmentation strategy is used in case there is more the 18 follicles >= 11 mm. But to advocate that it should be used in all patients is not reasonable, since this can be done in other ways. The text has been adapted to underline that studies were not excluded but we did not analyze OHSS as an outcome. In the safety section, it is clearly stated that the risk of OHSS is lower in the freeze-all strategy.
Christos Venetis Efstratios Kolibianakis	39	1540	There is a solid underlying pathophysiological base that the intervention of elective freeze-all is more likely to be beneficial in terms of improving pregnancy rates in high responders, as high responders have been shown to have higher risk of elevated serum progesterone at the end of the follicular phase which in turn is known to be the only factor to have be shown to negatively affect endometrial receptivity during the fresh embryo transfer (but not subsequent frozen-thawed embryo transfers (Venetis et al., 2013, Human Reproduction Update). This is an important piece of information that should be present in these recommendations and should also be used to guide the interpretation of the evidence. Interestingly, the authors do state: "Four large cohort studies based on the SART, HFEA and Victoria (Australia) data have shown the same tendency that the freeze-all strategy seems to be beneficial in high responders but not in intermediate or low responders (Acharya et al., 2018, Le et al., 2022, Li et al., 2019b, Smith et al., 2019) " However, they do not take into consideration the only meta-analysis of RCTs analysing the value of the freeze all approach in patients with different types of ovarian response instead of cohort studies (Bosdou et al 2019, Human Reproduction). This represents an important oversight which leads to recommendations that are likely not applicable to all populations and could lead to harm for some patients (e.g. high responders/ PCOS).	Thank you for the relevant comment. We have now included the meta-analysis of RCTs analysing the value of the freeze all approach in patients with different types of ovarian response instead of cohort studies (Bosdou et al 2019, Human Reproduction).

Christos Venetis Efstratios Kolibianakis	39	1548	The authors state: "The most recent Cochrane meta-analysis found no difference in cumulative LBR between the “freeze-all” strategy and the conventional fresh ET (OR 1.08; 95% CI 0.95 to 1.22; 8 RCTs; n=4712; I^2=0%; moderate-quality evidence) (Zaat et al., 2021)." A recommendation on freeze all cannot be based on cumulative live birth as expressed on the study by Zaat et al. as it can bias the result in favour of the fresh embryo transfer group through effect dilution. The correct comparison would be either by comparing the result of the first intended embryo transfer or by comparing the number of live births produced by the entire cohort of embryos.	This matter is discussed in the paper and we do comment on the cumulative live birth rates reported in the Zaat review from 2021. The comparison on the first embryo transfer as the reviewer mentions is performed in the two RCT’s not included in any of the meta-analyses (Stormlund et al., and Maheshwari et al) and they find similar reproductive outcomes in normo-responders for freeze-all and fresh embryo transfer.
Christos Venetis Efstratios Kolibianakis	39	1554	The authors state: "The non-superiority of the freeze-all strategy was also confirmed in the two most recent RCTs performed in Europe on 460 and 619 patients (Maheshwari et al., 2022, Stormlund et al., 2020)." The superiority of a strategy cannot be judged only on the basis of whether it increases pregnancy rates. Increased safety can also render a strategy superior if pregnancy rates are comparable. The study by Stormund did not show a difference in the incidence of OHSS, however, 10.4 % of patients in the fresh ET arm were converted to a freeze all because of the risk of OHSS! The study by Maheswari was terminated prematurely and at that time the incidence of severe OHSS in the fresh embryo transfer group was 0% compared to 8.1% in the fresh embryo transfer group, the difference being statistically significant, in line with the meta-analysis by Bosdou et al (2019) which was not taken into consideration in the present recommendation. Assessing potential clinical superiority by not taking into consideration that significantly more patients in the fresh embryo transfer arm develop OHSS is highly misleading. Furthermore, as discussed previously, the freeze-all strategy has been shown to be superior even in terms of pregnancy rates in high responders (Bosdou et al., Human Reproduction, 2019).	The study by Stormlund et al., had the strategy to convert to freeze-all in case of a high risk of OHSS on the day of trigger and with that strategy 10.4% were converted and the OHSS risk was similar in the two groups. It is evident that fresh embryo transfer should only be performed with a strict cancellation/segmentation strategy which is also written in the recommedations paper and has now also been added to the recommendation that with a fresh embryo transfer strategy there should be strict cycle segmentation criteria to avoid OHSS. Regarding the Maheshwari et al., 2022, they had no clear segmentation strategy explaining the high risk of OHSS in the fresh arm. It has been discussed in the recommendations paper that freeze-all can avoid OHSS but to claim that elective freezing is the way to go, when we can convert 10% and avoid OHSS is not reasonable based on the current literature.
Elena Kostova	39	1555	In principle, Stormlund et al 2020 is already included in the systematic review by Zaat et al (not in the cLBR analysis but in additional analysis: live birth rate)	Thank you, this has been clarified in the text.

Christos Venetis Efstratios Kolibianakis	40	1562	Regarding safety, the recommendation does not comment on large registries showing that the increase incidence of hypertensive disorders macrosomia and LGA are associated with the type of endometrium preparation for frozen embryo transfer and not with the transfer of frozen embryos (Ginstrom 2019, Saito 2019) Moreover, it does not refer to the studies that have shown the importance of the absence of corpus luteum during endometrium preparation for embryo transfer (von Versen-Hoynck et al 2019). Finally, the authors seem to emphasize the additional risks present with frozen embryo transfers (which are already performed and will continue to be performed) but do not consider at all in their recommendation the risks that could be mitigated by avoiding a fresh transfer, such as the increased risk of preterm birth, small-for-gestational age babies and placentation anomalies. Whether it is preferrable to have preterm deliveries and small-forgestational babies compared to large for gestational babies is not something that can be easily decided and requires a formal burden of disease analysis (Venetis, 2022, Human Reproduction).	The scope of this review was not to compare different FET endometrial preparation protocols and therefore we did not comment on the various FET protocols and their individual obstetric and perinatal risk profiles as this does not change the overall recommendation. We have now added the Busnelli syst review 2022 to the guideline. Further we have stated that the risk of preterm birth and SGA is lower after FET.
Carlos Calhaz-Jorge	40	1571	"…strategy compared to compared to the …"	This was corrected in the text.
Arianna D'Angelo	40	1571	remove one "compare"	This was corrected in the text.
Christos Venetis Efstratios Kolibianakis	40	1575	The authors of the recommendation assume that time to pregnancy is a major determinant when patients are making decisions regarding their treatment. They, however, present no evidence to substantiate this hypothesis. On the contrary, there is recent evidence published (which the authors do not take into account) that clearly indicate the opposite, i.e. that couples' preferences are driven by anticipated chances of live birth, miscarriage, neonatal complications, and costs but not by the differences in the treatment process including delay of embryo transfer linked to frozen embryo transfer (Abdulrahim et al., 2021, Hum Reprod). Therefore, the authors argument that because time to pregnancy is likely to be longer in the freeze-all arm, this approach is not recommended, is not justified and should be revisited on the basis of the whole body of evidence.	This is very speculative. Why should pregnancy be postponed when there is absolutely no reason to justify an add-on procedure apart from adding a freezing procedure to the treatment that is unnecessary. This question was asked to the patients and their responses were clear that they would accept freeze-all in case of a high risk of OHSS (Stormlund et al., Hum Reprod 2019). The WG decided not to enter this debated to the guideline.
Cristina Magli	40	1586	Is this true for both HRT and natural cycles?	yes, this is true for both HRT and natural cycles
25. ICSI FOR NON-MALE FACTOR INFERTILITY				
Cristina Magli	41	1626	I suppose that the majority of these data come from male factor infertility, so do we know whether the recorded defects are related to ICSI or to the infertile condition?	This was corrected in the text.
Elena Kostova	41	1635	Leunens et al., 2006 is not really recent	Adapted as suggested by the reviewer.
Carlos Calhaz-Jorge	42	1640	I think the word "early" is illogical here. We would be influenced that it was a less relevant study because old (2014) but, then, the emphasis is on the results of a meta-analysis published in 2014.	Adapted as suggested by the reviewer.
Cristina Magli	42	1655	Why "should not be recommended" instead of "is not recommended"?	Adapted as suggested by the reviewer.

26. ANTIOXIDANT THERAPY				
Elena Kostova	42	1670	It is “very-low quality evidence”	This was adapted as suggested.
Elena Kostova	43	1691	Based on the results presented in both Cochrane reviews and cited here, I agree with the recommendation. You could focus more on the fact that the quality of the evidence was very low in both reviews. For example, Ligny, et al 2022 report “When studies at high risk of bias were removed from the analysis, there was no evidence of increased live birth (Peto OR 1.22, 95% CI 0.85 to 1.75, 827 men, 8 RCTs, P = 0.27, I2 = 32%)”.	This information was added to the paper.
Cristina Magli	43	1693	Considering the results reported under "Efficacy", I would reformulate this recommendation.	Sensitivity analysis showed uncertain effect of antioxidants on LBR in females, and no evidence of an effect on LBR in males. This information has now been added to the paper.
27. COMPLEMENTARY AND ALTERNATIVE MEDICINE				
Elena Kostova	43	1713	The reference Lim et al 2016 seems redundant (review was updated in 2019)	The reference was omitted as suggested.
Chi Chiu Wang	43	1714	It should be also covered as one of potential treatment even though the evidence is limited, but worth to mention and describe.	Unfortunately, the WG could not find what the reviewer was referring to.
Elena Kostova	44	1730	I think the included study Wu et al 2017 did not include patients undergoing ART, but patients who received clomiphene	The meta-analysis was excluded from the body of evidence.
DISCUSSION				
Danilo Cimadomo Antonio Capalbo	45	1782	“In general, there is a need for more basic research in the field of MAR, for example with regards to the immunological and inflammatory processes during implantation and pregnancy and the relevance of the genetic composition of the embryo.” What do the authors mean by "genetic composition of the embryo"? If you imply "chromosomal", we think that there is substantial body of evidence in both the academic and clinical fields supporting that embryonic aneuploidies are the (currently known) single most important cause of implantation failures, miscarriages, and chromosomal syndromes in humans, especially if meiotically (mostly maternally) derived abnormalities. Although more RCTs are perhaps needed to better quantify the clinical benefits and the absence of an impact of aneuploidy testing (at the blastocyst stage and without reporting alleged mosaicism) in patients with a clear indication to PGT-A, we think that "genetic composition of the embryo" cannot be grouped together with "immunological and inflammatory processes " in terms of our current limited knowledge regarding a putative impact on implantation and pregnancy.	The sentence has been reformulated.
Ainsley Newson Siun Gallagher Wendy Lipworth	45	/	The Discussion could include mention of the importance of ongoing consumer engagement and education regarding add-ons. This will help align consumer expectations with the recommendations.	A patient leaflet will be published with the recommendations paper.

Ainsley Newson Siun Gallagher Wendy Lipworth	/	/	The Discussion could also note expectations regarding marketing and advertising of add-ons.	The WG considered this outside the scope of this recommendations paper.
GENERAL COMMENTS				
Roy Farquharson	/	/	A welcome addition to ESHRE and it's comprehensive display of GPRs and GDLs This topic has been thoroughly researched and analysed by a pantheon of ESHRE members to provide an objective direction of travel for those involved in delivering MAR to less knowledgeable patients and relatives The reviewers are to be congratulated on displaying all the best Thucydidean virtues of objective detachment and application of sensible analysis while being concise and well informed.	Thank you for these kind words.
Bryan Woodward	/	/	Thank you so much for providing this valuable good practice document. We've been crying out for it, and now we have it.	Thank you for these kind words.
Carlos Calhaz-Jorge	/	/	A very comprehensive and well written text. An amazing work. Congratulations and thanks to the authors	Thank you for these kind words.
David Cahill	/	/	I am overwhelmingly impressed by this document and I am impressed that the authors have not been swayed or influence by the potential conflicits of interest that must arise from those clinics who use many of these unfounded treatments which are provided at some cost to couples having treatment. I have almost nothing to say that is negative about this and am so pleased you have provided it. I hope it will not be diluted after review.	Thank you for these kind words.
Arianna D'Angelo	/	/	Many thanks for producing this very useful overview on the "IVF shopping list " very much needed. I feel that the adds on below are missing from the list: Dual trigger is missing from the list of adds on why? Since a section is dedicated to antioxidants, maybe a section should be dedicated to effect of vitamins and supplements such as inositol, vit D, coenzyme Q and so on. It might be worth having a section only for supplements. This is frequently asked by patients and surely highly commercial area of business.	Thank you for the suggestion. At this stage, this topic cannot be added to the current recommendations paper. However, we will keep it in mind for the update or the extension of the paper.
Ainsley Newson Siun Gallagher Wendy Lipworth	/	/	We applaud ESHRE and the working group for the significant work that has been undertaken to produce this important document. We hope that this document has a positive impact on clinical provision of ART.	Thank you for these kind words.
Ainsley Newson Siun Gallagher Wendy Lipworth	/	/	An 'at a glance' table showing each add-on and the recommendation made would be beneficial. Sometimes there are multiple recommendations within each add-on, which may be confusing. We suggest each recommendation is numbered. This will enhance ease of reading and use of these Good Practice Recommendations	An overview table of all recommendations will be included as an supplementary data II in the final version of the recommendations paper
Aboubakr Mohamed Elnashar	/	/	Excellent and comprehensive into 1. Diagnostic tests 2. Lab test and interventions 3. Clinical management	Thank you for these kind words.

Pavel Trávník	/	/	The authority of ESHRE could bring very negative effects in the case, where not fully correct statements are published. Not well- founded statements could be misused by governments and/or insurance companies for restrictions in patient care.	ESHRE and the expert working group have prepared the recommendations after careful consideration of all relevant evidence, with focus on published data where available but also including professional experience and expert opinion where relevant. We do not consider any limits with regards to the implementation of add-ons of particular concern with regards to patient care. However, the document will be updated when more data would become available, and consequently policies may need to be adapted in the future.
Pavel Trávník	/	/	In general, many recommendations in ESHRE_ADD-ONS draft are not correct being based on wrong selected publications and tainted by non-medical and non-scientific convictions. Some of them are not clearly expressed.	In addressing the comments received during the stakeholder review, we have clarified the reasoning for some recommendations. If we have not used what could be considered the most relevant references it may be that they were not published as peer-reviewed papers. If for some reason an important reference was missed during the literature search, the experts participating in the stakeholder review process had the opportunity to alert the working group who would have considered the publication and where needed adapted the recommendation.
Pavel Trávník	/	/	Because this criticism does not apply to only minority of ESHRE_ADD-ONS draft articles, I suppose to retract this material completely. I suppose give only that kind of recommendations, where the content is doubtless from the medical and scientific point of view, not being result of subjective belief or interest. In case of uncertain information or existing controversial data there is necessary give no recommendation	We understand that the reviewer would prefer no recommendations on the topic, but ESHRE does consider it important to have an open discussion about the lack of supporting data for the different interventions offered and considers it relevant to take a position and recommend against offering these interventions to patients (and asking them to pay for it) until high quality evidence is available.

Bryan Woodward	/	/	Throughout the texts, please either use consistent English-English or US-English. If the former, please use “fertilise” rather than “fertilize”	This was adapted as suggested.
Zuzana Holubcová	/	/	I do appreciate that the presented guideline covers a wider spectrum of so-called „adds-on“procedures than the HFEA traffic light system and is based on a more elaborate review. However, it is merely a review of literature that often pools together published evidence of different quality. I would like to point out that apart from publications there is empirical experience and internal validations available in the ART community. Only a tiny minority of clinicians publish their observations, the reason being a lack of time, experience with academic writing, and availability of financial resources to cover publication fees. I would suggest ESHRE produced more surveys and ask the IVF community about the experience and validation data, not only relying on published evidence (of variable quality). For adds-on procedures which are applied only in rare diagnosis cycles is very difficult to collect meaningful data within a single IVF unit. Hopefully, the development of the EuMAR registry will help to pool anecdotal reports in the future and there will be experienced researchers available to perform data analysis and publication writing.	As explained in the methods section, priority was given to systematic reviews and RCTs, and observational data were included for specific populations where no RCT was available. This recommendations paper was developed according to the ESHRE manual for development of good practice recommendations.
Zuzana Holubcová	/	/	Another major concern I have is the overall tone of the document. The „add-ons“ are described as money-driven malpractice. The authors emphasize that procedures that are not evidence-based should not be practiced. How can we collect data if we do not make effort to implement new strategies? Innovation is driving development! Why not give a shot to unconventional procedures instead of sticking to routine approaches only or directing the patient to the donor cycle after multiple failed attempts? You should distinguish between selling false claims about higher cPR or LBR for all from targetted treatments of rare diagnosis patients (e.g. AOA, sperm motility enhancement, mitochondrial therapy). Some add can make a difference for poor-prognosis patients. A more positive attitude to innovative strategies from a respected professional organization could ease obtaining the national control body´s permission to run experimental treatments under research conditions (I am speaking from experience here). The fact that innovation must be introduced in the experimental regimen (ethical approval, informed consent, long-term follow-up) should be more emphasized. Covering extra charge is debatable, the occasional application of an "add-on" procedure as a last-chance treatment can not be compared with clinical trials sponsored by the pharmaceutical industry. As long as patients are fairly informed about the character of treatments, potential risks and benefits, and informed consent is signed, I see no ripoff or misconduct.	The discussion has been adapted to encourage more research. If an intervention has been shown to be beneficial in a specific patient population, this is mentioned in the recommendation.

Ainsley Newson Siun Gallagher Wendy Lipworth	/	/	We support the recommendations that attach future use with research. commercial providers who currently offer the add-ons reviewed may experience a drop in revenue as a result of these recommendations. The 'research' that is recommended will require funding and infrastructure. As such, we feel the document could be stronger in its encouragement of commercial providers in becoming involved in research. As a part of this, ESHRE could also champion the need for dedicated funding streams, which will help ensure the generation of quality evidence while also supporting responsible innovation.	The discussion has been adapted to encourage more research.
Ainsley Newson Siun Gallagher Wendy Lipworth	/	/	There are around eight instances in the document where a recommendation regarding an add-on is such that it can be used in certain circumstances. In these instances, a statement could be added that monitoring is still advised, to contribute to the longer-term evidence base.	This was added to the relevant recommendations.
Ainsley Newson Siun Gallagher Wendy Lipworth	/	/	Consistent with our comment #3, inter-provider and international collaboration should be encouraged, including sharing research results. This will optimize the generation and synthesis of quality evidence.	This is acknowledged in the discussion of the recommendations paper.
Danilo Cimadomo Antonio Capalbo	/	/	We think that clinical strategies (like many of the add-ons listed here are) may be beneficial in certain populations of patients and/or economical-social-clinical settings. In our view, the working group can be more tolerant towards some of them, rather than stating "NOT recommended". Perhaps a score of risks and benefits (1 to 5 or 1 to 10) can be adopted.	In circumstances where an intervention is not routinely recommended, but can be considered in a specific patient population, this is indicated in the recommendation.
Danilo Cimadomo Antonio Capalbo	/	/	We think that the document may benefit from some summary tables and/or figures for all topics, and not only for PGT-A.	A summary table with the recommendations and the quality and strength of the evidence will be published as Supplementary data II with the recommendations paper.
Ramos Liliana	/	/	Preference to add a recommendation per item, sometimes the structure differs per add on	The WG reviewed the recommendations and have now used 4 standard sentences.
Antonio Requena Vanessa Vergara Nicolás Prados	/	/	We are in general agreement of the document, although it is not equal a non-recommendation or an insufficient data for a general recommendation. Many of the studies depend on specific patient profiles and the experience or expertise of a specific center. We obviously need clear evidence from meta-analysis to recommend an add-on in general, but this should not preclude that in a specific setting for specific patients the technique proves useful.	In circumstances where an intervention is not routinely recommended, but can be considered in a specific patient population, this is indicated in the recommendation.
Chi Chiu Wang	/	/	Lacking, suggest to include some flow chart of recommendation with evidence level as in ESHRE GOOD PRACTICE RECOMMENDATIONS ON RECURRENT IMPLANTATION FAILURE for reference ease.	A summary table with the recommendations and the quality and strength of the evidence will be published as Supplementary data II with the recommendations paper.

Mark Larman	/	/	It should be recognized that procedures performed at the end of a process (i.e., time of transfer) are not “silver bullets”. They will be dependent on the viability of the transferred embryos, which is dependent on the inherent viability of the gametes and subsequent in vitro culture. If these are compromised/suboptimal a procedure is unlikely to improve outcomes for patients. The relative lack of standardization and variable clinical outcomes reported in IVF make it challenging to robustly demonstrate efficacy of a particular device/process, especially when it is used at the end of the procedure.	The difficulties inherent to research in this field (and specifically add-ons applied near the time of embryo transfer) is considered outside the scope of the current paper.
Alan Thornhill	/	/	While I don’t necessarily disagree with some of the comments made throughout the document – notably the introduction and methods section, I don’t believe an esteemed organisation such as ESHRE should be publishing ‘opinions’ under the guise of professional guidelines where there is evidence available to back up those claims and opinions. I have worked with ESHRE and other organisations to develop guidelines and thus have some experience of the process. While I accept the process can be challenging, I don’t think it is good practice to take short cuts. Overall, my main issue with the paper as it stands is the inconsistencies in language, format and methodology throughout. In this sense, in its current form, I believe the paper to have fundamental flaws which must be addressed prior to publication.	Given the lack of research and published data on several of the topcis, the procedure for evidence-based guidelines would not be appropriate, nor feasible for this topic. For the sake of transparency to the reader, the document was developed as a good practice recommendation document, which is clearly based on expert opinion in addition to the evidence. The ultimate aim would be to stimulate research (on some of the add-ons) to be able to provide a decent evidence base for future evidence based guidelines.
Alan Thornhill	/	/	In summary, it is clear that a large amount of work has gone into reviewing data and publications but the conclusions (including but not limited to the specific examples in the two categories of ‘safety’ and ‘recommendations’) are let down by inconsistency and imprecise language. As a reader and author of guidelines I know first-hand the impact they can have on professionals trying to do the right thing for patients and according to evidence and, in some cases, the reasoned opinions of their peers. It is critical that these guidelines are presented in the most transparent, balanced and accurate fashion to have the maximum impact on clinicians and, ultimately, their patients. A patient being steered away from an ineffective, expensive treatment is a noble aim and a good outcome. A patient not having a treatment which could have delivered a successful outcome because of a misinterpreted guideline is something which we would all wish to avoid.	The WG has reviewed the efficacy and safety sections, to make sure they are as consistent as possible. Furthermore, this recommendations paper has been developed according to a published methodology (Vermeulen et al., 2019).

Christos Venetis Efstratios Kolibianakis	/	/	Throughout this recommendation but also in the case of elective freeze all the formulation of recommendations does not follow the ESHRE procedures as described in the corresponding manual. According to the manual: "Recommendations can be formulated as strong recommendations, or conditional recommendations, indicating whether the recommendation is applicable for all situations, or whether there is uncertainty and shared-decision making is recommended." On the contrary the authors formulate the recommendation as follows “As the freeze-all strategy is not superior to fresh embryo transfer in terms of cumulative live birth rate, live birth rate and ongoing pregnancy rate, while time-to pregnancy is likely to be longer, elective freeze-all is not recommended".	The recommendation is applicable to all situations where freeze-all is used as an add-on.
Sarah Lensen Andy Vail Jack Wilkinson	/	/	The guideline might benefit from a table which summarises the overall recommendations for each of the 27 add-ons reviewed	A summary table with the recommendations and the quality and strength of the evidence will be published as Supplementary data II with the recommendations paper.
Tarek El-Toukhy	/	/	Overall a good guideline document	Thank you for these kind words.
Ahmed Fawzy Galal	/	/	Up to date recommendation in a hot topic	Thank you for these kind words.
Sarah Lensen Andy Vail Jack Wilkinson	/	/	At times the guideline appears to take the conclusions of research articles at face-value without consideration for the methodological rigor of the study or whether the study’s conclusions are indeed supported by the study results. For example, - For TLI, the safety section states “Kirkegaard et al. concluded that TLI was as safe as embryo culture in conventional incubators”. Do the ESHRE guideline reviewers endorse this conclusion, then? What is the conclusion based on – what safety parameters were measured? This sentence seems to suggest the authors of this guideline have not given any consideration to critically appraising this conclusion. - Please see comments related to the use of data from observational studies or systematic reviews that contain them - The paper states “The test and pET seemed however to increase the cumulative LBR that considered both the first ET and cumulative rates after 1-year follow-up” (page 5, line 197). This analysis is invalid as described in the Lensen 2021b paper referenced. It doesn’t seem sensible therefore to state that the results of this analysis show an increase in cumulative LBR.	In the TLI section, the wording was amended. For the endometrial receptivity testing, both the criticism and the author’s reply have been included in the section. A newer RCT also showed no benefit.

Sarah Lensen Andy Vail Jack Wilkinson	/	/	The authors make the error of concluding that “no evidence of a difference” is the same as “evidence of no difference” when results are imprecise and inconclusive. Examples - “The absence of an improvement in LBR was confirmed in a large multi-centre study published the same year (HABSelect study; OR 1.12; 95% CI 0.95 to 1.34; n=2772; p=0.18) (Miller et al., 2019).” This result does not demonstrate an absence of an improvement. The confidence interval is consistent with the possibility of a notable benefit, a small disadvantage, or anything in between. It would be more appropriate to state that “the effect on live birth remained unclear in a large trial” or similar. In fact, there was clear evidence of a reduction in miscarriage per woman randomised in the study, and this was one of a small number of prespecified secondary outcomes. The following recommendation that “PICSI is not recommended as a sperm selection method since it has been shown to have little or no effect on live birth or clinical pregnancy rates” is not supported by the randomised evidence. This is not what the confidence interval from this study tells us. Absence of statistical significance does not mean that there is “little or no effect”. - “A recent Cochrane review confirmed that addition of GM-CSF in the embryo culture medium did not increase LBR (OR 1.19, 95% CI 0.93 to 1.52; 2 RCTs; n=1432; I^2=69%; low quality evidence).” This wide confidence interval is consistent with the possibility of a large increase – the point is that we remain uncertain. The result does not show that there is no effect of this add-on.	This has been checked throughout the recommendations paper and amended where necessary.

Josie Hamper	/	/	I have read this guidance with a particular interest in the perspectives and experiences of IVF patients. I have recently completed a large qualitative study on IVF patient experiences of treatment, which specifically considered their decision-making practices around treatment add-ons. This was part of a research project led by Dr Manuela Perrotta at Queen Mary University of London. While the ESHRE guidance document is not directed at IVF patients, I believe many patients will find this guidance and use it to inform their evaluations of add-ons. You may be interested in two journal articles that I have co-authored with Dr Manuela Perrotta. These articles empirically contextualise the difficult decisions that patients have to make in relation to choosing whether to pursue add-ons. In both of these articles we explore how patients make decisions about add-ons in a context where there are many unknowns about the efficacy of treatments. We confirm that in the context of privately funded IVF, paying for even a small possibility of improved chances of pregnancy has strong appeal. The guidance refers to these dynamics on page 2, lines 78-81. Perrotta, M. and Hamper, J. (2021) The crafting of hope: Contextualising add-ons in the treatment trajectories of IVF patients. Social Science and Medicine, 287. Perrotta, M. and Hamper, J. (2022) Patient informed choice in the age of evidence-based medicine: IVF patients' approaches to biomedical evidence and fertility treatment add-ons. Sociology of Health and Illness, [online first]. I hope this may be of interest to the group.	Thank you for this interesting information, however, it is considered outside the scope of this recommendations paper.
Sarah Lensen Andy Vail Jack Wilkinson	/	/	The authors of this document have brought together a vast amount of research; it is an impressive amount of work and we are very supportive of this initiative by ESHRE.	Thank you for these kind words.

Sarah Lensen Andy Vail Jack Wilkinson	/	/	It is not always clear whether the referenced systematic reviews include data on RCTs or observational studies, or both. This has huge implications for the importance of this data and the reader would therefore benefit from this information. For example in the case of PRP Line 1013 the referenced review (Maleki-Hajiagha et al., 2020) includes 7 studies of which 4 are cohort studies. The pooled effect is provided for these 7 studies as per the review, but then not for the 7 RCTs referenced as being published since. In doing so, this is giving more weight to the observational studies simply because they were included in a systematic review. It should be clear for each treatment effect provided, whether the data were produced from RCT, observational data, or both. Further, combining the results of RCTs and observational studies into a single pooled estimate in meta-analysis is inappropriate (see Cochrane Handbook '24.6.2.1 Combining studies'). This ESHRE guideline should not be seen to endorse this methodological error or the consequent results, by giving specific reference to pooled effects generated by reviews that have done this e.g. Maleki-Hajiagha et al., 2020 in the case of PRP and Cao et al 2018 in the case of hysteroscopy, and probably others. When utilizing any data from observational studies, it is important the results are adjusted for possible confounders. In many instances, the included systematic reviews have undertaken meta-analysis where unadjusted estimates were used; this data is very unreliable and should be specifically noted as such in this guideline or else not used to inform the recommendations. For example, - Gao and Hosseini studies cited in Cao 2018 (hysteroscopy) report only unadjusted analyses, and these data have been pooled together (and with RCT data!) and cited in this recommendation - For Rescue-IVM. "In a prospective cohort study, 146 poor prognosis patients received rescue IVM (n=50) or double ovarian stimulation (n=96) (Liu et al., 2020b). Comparing the IVM part in group 1 with the luteal phase stimulation part in group 2, there was no significant difference seen in live birth (10% vs. 16.9%) or clinical pregnancy rate (10% vs. 21.5%)". These results have not been adjusted for confounding. Good-quality nonrandomsied evidence can indeed be useful in some cases, but any estimate which is not adjusted for confounding is critically flawed (BMJ 2016;355:i4919). Pooling several critically flawed estimates does not improve the situation in any way – it compounds the problem, and gives the misleading impression that critically flawed results represent high-quality data. - In relation to PGT-A the document cites Zheng et al 2021 to support the suggestion that PGT-A affects perinatal outcomes. The meta-analyses in this review included results from nonrandomised studies that are completely unadjusted for confounding, and have limited value. Although the authors use softer language when presenting the results of observational studies such as stating the results "appear to show" – this will still be interpreted as benefit by most readers, and in many instances the authors do not use such soft language e.g. Line 203 page 5 "which proved to have a larger effect on implantation rate". This will be a very influential guideline and unreliable studies and results should not contribute to the discussions and recommendations with the weight that they currently do. If a distinction had been made between high and low-quality nonrandomized evidence the situation would not be quite so serious. But no such distinction has been made.	This has been clarified in the text.

Sarah Lensen Andy Vail Jack Wilkinson	/	/	The subheading of “Other aspects” seems to have been used inconsistently. - For Microfluidics (line 778…) this section seems to contain what would be viewed as background information about this add-on. - In the ‘Other aspects’ section of TLI it discusses that clinics advertise TLI on their websites…. This is true of most add-ons so why (only) mention it here? - Cost is mentioned for some add-ons but not all - Etc.	We agree that this section is indeed used inconsistently to summarize the information taken into consideration in drafting the recommendations, apart from efficacy, safety. The WG has merged this section with the efficacy and safety sections where possible.
Sarah Lensen Andy Vail Jack Wilkinson	/	/	The wording of the recommendations appear inconsistent when the overall results of existing studies imply the same thing (no evidence of benefit). For example - “Both niPGT and mtDNA load measurements are to be considered in research phase” - “Due to the lack of clear benefit, endometrial receptivity tests are not recommended” “In vitro maturation is not recommended for infertile patients without specific indications (PCOS/high responders or fertility preservation) in absence of long-term safety data, procedural reliability, and effectiveness.” So is it recommended for PCOS/high responders or fertility preservation then?	The WG has reviewed the recommendations and has used 4 standard phrases.
Veljko Vlaisavljevic	/	/	there is one important part missing from the document. This is the opinion on the status of aquired and congenital thrombophilia workup in ART patients (and, of course, the status of anticoagulant therapy). Has the working group avoided addressing and assessing this problem by any particular means ?. I certainly think this is an important chapter and it is a pity that it is not included. These recommendations will make much easier the work in project of the ESHRE -Centre certification for good clinical practice, as the quality of ART centres cannot be addressed without documents of this type. Otherwise, I am of the opinion that even the existing ESHRE guidelines are too little included in the evaluation platform of this project. I believe that your help and activity in the group of inspectors in this area would significantly raise the professional level of this important ESHRE project.	Thank you for the suggestion. At this stage, this topic cannot be added to the current recommendations paper. However, we will keep it in mind for the update or the extension of the paper.
Forest Garner	/	/	Please also consider the transfer of a second embryo (fresh or frozen) as an add-on. This is no longer the norm in the USA, and in my opinion should not be the norm anywhere. It is associated with a spectrum of risks greater in severity than any of those compared in fresh vs freeze-all. A decade ago, Dr. Bradley van Voorhis, former President of SART, called the transfer of a second embryo “the most dangerous thing we do in IVF”. Please do not ignore it here.	Thank you for the suggestion. At this stage, this topic cannot be added to the current recommendations paper. However, we will keep it in mind for the update or the extension of the paper.
Jean Calleja Agius	/	/	The addition of embryo culture at hypoxic levels, and what level of hypoxia	Thank you for the suggestion. At this stage, this topic cannot be added to the current recommendations paper. However, we will keep it in mind for the update or the extension of the paper.

Jean Calleja Agius	/	/	Measurement of cytokines	Thank you for the suggestion. At this stage, this topic cannot be added to the current recommendations paper. However, we will keep it in mind for the update or the extension of the paper.
Jean Calleja Agius	/	/	Comment one embryo culture at hypoxic levels	Thank you for the suggestion. At this stage, this topic cannot be added to the current recommendations paper. However, we will keep it in mind for the update or the extension of the paper.
Attila Vereczkey	/	/	Extended Blastocyst culturing would be an important issue to add Multivitamin supplementation issue would be also suggested to add Dietary suggestions like high protein diet etc. would be also interesting to add US guided Embryo Transfer would be important to add as well.	Thank you for the suggestion. At this stage, this topic cannot be added to the current recommendations paper. However, we will keep it in mind for the update or the extension of the paper.
Ahmed Samy Saad	/	/	Saline infusion sonography or sonohysterography should be added in the investigations before hysteroscopy. It has an added value to the diagnostic tests and more simpler	Thank you for the suggestion. At this stage, this topic cannot be added to the current recommendations paper. However, we will keep it in mind for the update or the extension of the paper.
Ahmed Samy Saad	/	/	Hormonal monitoring of the ovarian stimulation with the ultrasound follow up or Should be added ultrasound alone should be added as no rule and still many use it	Thank you for the suggestion. At this stage, this topic cannot be added to the current recommendations paper. However, we will keep it in mind for the update or the extension of the paper.
Ahmed Samy Saad	/	/	ET under clinical touch or ultrasound guided Should be added as no rule	Thank you for the suggestion. At this stage, this topic cannot be added to the current recommendations paper. However, we will keep it in mind for the update or the extension of the paper.
Ahmed Samy Saad	/	/	Group or single culture Should be added as no rule and still many use it	Thank you for the suggestion. At this stage, this topic cannot be added to the current recommendations paper. However, we will keep it in mind for the update or the extension of the paper.

Ahmed Samy Saad	/	/	Bed rest after ET or not Should be added as no rule and still many use it	Thank you for the suggestion. At this stage, this topic cannot be added to the current recommendations paper. However, we will keep it in mind for the update or the extension of the paper.
J. Smitz	/	/	Non-invasive Cumulus cell gene expression test	Thank you for the suggestion. At this stage, this topic cannot be added to the current recommendations paper. However, we will keep it in mind for the update or the extension of the paper.