Scientific and Clinical Advances Advisory Committee (SCAAC) – Matters arising

Monday 05 February 2024

Date	Action	Responsibility	Due	Progress to date
31/01/2022	Assess whether further outputs are required on the topic of the impact of the microbiome, and whether it needs to be considered as a treatment add-on.	Mina Mincheva, Policy Manager	Closed	The topic 'Impact of microbiome on fertility treatment outcomes' was discussed by the Committee at the October 2023 SCAAC meeting. The Committee recommended that testing of the microbiome and/or the use of treatments which claim to modulate the vaginal and/or endometrial microbiome should not be considered for inclusion on the add-ons list at this time.
06/06/2022	The Executive will amend the treatment add-ons application form and decision tree for considering applications for additional add-ons in line with the updated treatment add-ons rating system. SCAAC can then reconsider the application for Androgen supplementation as a treatment add-on.	Dina Halai, Head of Policy	Ongoing	The Executive are in the process of amending the treatment add-ons application form and decision tree. The application for Androgen supplementation as a treatment add-on will then be brought to a future meeting of the SCAAC for reconsideration.
03/10/2022	Consider a framework for assessing AI technologies which fall within the regulatory remit of the HFEA.	Mina Mincheva, Policy Manager	Ongoing	AI will be discussed at the February 2024 SCAAC meeting. The Executive have had a watching brief on developments in the uses of

	Publish a Clinic Focus article for the sector on developments in the regulation of AI.			AI within clinics, including regular engagement with other relevant regulatory bodies, for some time. The Executive is considering outputs needed going forward, including communication activities aimed at the clinical and research communities.
25/07/2023	Executive to update the website information for patients about treatment add-ons to reflect new ratings recommended by SCAAC members in July 2023.	Dina Halai, Head of Policy	Closed	The updated website add-ons information and related consensus statement went live on 19 October 2023 and was accompanied by a media campaign. Based on feedback received from the sector, the Executive will make minor changes to the patient information on our website to make it more explicit for patients.
25/07/2023	Three HFEA Authority members of SCAAC together with a SCAAC adviser will visit Newcastle Fertility Centre to hear about the organisation and staffing of the mitochondrial donation programme in more detail.	Dina Halai, Head of Policy	Closed	Members of the SCAAC visited to Newcastle Fertility Centre on 14th December 2023. An update on the visit will be provided at the February 2024 meeting.

Horizon scanning and prioritisation of issues

Details about this paper

Area(s) of strategy this paper relates to:	Shaping the future
Meeting:	Scientific and Clinical Advances Advisory Committee (SCAAC)
Agenda item:	6
Paper number:	HFEA (05/02/2024) 006
Meeting date:	05 February 2024
Author:	Emily Staricoff, Policy Manager (Science and Engineering Fast Stream)
Annexes	Annex A: Briefings on key issues identified during horizon scanning Annex B: Spreadsheet of papers identified through horizon scanning Annex C: Topic prioritisation table Annex D: Committee workplan 2024-2025 Annex E: Committee purpose and function as per HFEA standing orders

Output from this paper

For information or recommendation?	For recommendation
Recommendation:	Members are asked to: • consider the issues identified as high, medium, and low priority through the horizon scanning process; • consider the recommended committee workplan for 2024/2025; • consider whether advice from additional external advisors would help in achieving the work recommendations; • consider the frequency of review for treatment add-ons
Resource implications:	Subject to committee recommendations
Implementation date:	As per committee workplan for 2024-2025 (Annex D)
Communication(s):	N/A
Organisational risk:	Low

1. Background

1.1. The Authority established a horizon scanning function in 2004 to identify and monitor emerging and ongoing priority topics that could impact upon the field of assisted reproduction or embryo research. By identifying these topics, the Authority can be aware of potential implications for licensing and regulation arising out of such developments and prepare, if necessary, a policy position or relevant patient information.

1.2. Topics are identified from journal articles, relevant publications, conferences, and communication with an international group of experts who attended the Authority's Annual Horizon Scanning meeting during the respective year to discuss developing and future technologies within the fertility sector.

1.3. The horizon scanning process is an annual cycle that feeds into the HFEA Scientific and Clinical Advances Advisory Committee (SCAAC) business planning, and the Authority's consideration of scientific and ethical issues and standards.

2. Prioritisation process

2.1. A full list of publications identified during the 2024 horizon scanning process, including abstracts and journal impact factors, can be found in the spreadsheet that forms Annex B to this paper.

2.2. The PubMed search strings used for some of the topics were expanded during the 2024 horizon scanning process, aiming to increase comprehensiveness. For most topics, searches were based on title and abstracts only. Over the coming year, the Executive will continue to standardise the horizon scanning process.

2.3. To help with business planning, it is important for the Executive to be fully aware of topics that members consider to be high priority. Topics are categorised as **high**, **medium**, or **low priority** using the following criteria:

- Within the HFEA's remit
- Timescale for likely introduction (now or within 3 years)
- High patient demand/clinical use if it were to be introduced
- Technically feasible
- Ethical issues raised or public interest

2.4. Topics are **high priority** if they are within the HFEA's remit and meet at least two other criteria. High priority categorisation is also given to established techniques or issues that fall within the HFEA's remit and require ongoing monitoring or provision of patient information.

2.5. Topics are **medium priority** if they are within the HFEA's remit and meet one other criterion, or are outside the HFEA's remit but meet at least two other criteria.

2.6. Topics are **low priority** if they meet one criterion but are outside the HFEA's remit and unlikely to impact on research or treatment in the near future.

2.7. A table detailing the topic prioritisation decisions is provided in Annex C.

2.8. The frequency at which topics are discussed by the committee is determined by their priority, with high priority topics being discussed most frequently (see Annex D for committee workplan).

3. High priority issues

3.1. The Executive considers the following topics (listed in alphabetical order) to be high priority for 2024-2025:

- Alternative methods to derive embryonic and embryonic-like stem cells
- Artificial intelligence (AI), robotics and automation in fertility treatment (previously named 'artificial intelligence (AI), robotics and automation')
- Emerging technologies in embryo and gamete testing (previously named 'new technologies in embryo and gamete testing')
- Germline genome editing (previously named 'genome editing')
- Impact of long-term cryopreservation of gametes and embryo
- In vitro derived gametes
- Scientific considerations relevant to the '14-day rule' (input may be requested by the Authority as part of Act reform work)
- Stem cell-based embryo models (previously named 'synthetic embryo like entities')
- Testicular tissue transplantation to restore fertility in males (new topic suggested for introduction, see section 3.3 below and briefing in Annex A)

3.2. Based on this year's horizon scanning findings, short briefings on key developments in two high priority topics can be found in Annex A to this paper. Briefings were only written if a new topic was suggested for introduction, or if the Executive wanted to highlight significant advancement ahead of when a topic is next discussed as per the committee workplan (Annex D).

3.3. Considering the recent developments, highlighted in Annex A, in immature testicular tissue transplantation to restore fertility in adult males who are survivors of gonadotoxic treatment in pre-puberty, the Executive considers 'testicular tissue transplantation to restore fertility in males' topic to be distinct from the 'in vitro derived gametes' topic. The Executive recommends this topic is introduced as a new topic for horizon scanning.

3.4. During the horizon scanning process, the Executive noted the increasing overlap between the 'AI, robotics and automation' topic with other topics. To avoid repetition, only studies with AI, robotics and automation as a primary focus were included in the AI, robotics and automation topic. Studies that referred to AI, robotics or automation as a secondary method or outcome were included in the respective topic.

4. Medium priority issues

4.1. The Executive considers the following topics (listed in alphabetical order) to be medium priority for 2024-2025:

- Health outcomes in children conceived by ART (including the impact of culture media)
- Impact of the microbiome on fertility and fertility treatment outcomes
- Mitochondrial donation
  - This topic meets four of the five criteria therefore qualifies for high priority status. However, given that in **July 2023** the SCAAC received an update from the team at Newcastle Fertility Centre at Life (currently the only clinic in the UK with a HFEA licence to perform pronuclear transfer (PNT)) and four SCAAC members visited Newcastle Fertility Centre at

Life in December 2023, the Executive proposes that it is not necessary for the SCAAC to receive another update for a year and therefore this topic be deprioritised.

5. Low priority issues

5.1. The Executive considers the following topics (listed in alphabetical order) to be low priority for 2024-2025

- Artificial wombs for early or whole gestation (ectogenesis)
- Impact of stress on fertility treatment outcomes

6. Recommendations

6.1. Members are asked to:

- consider the issues identified as high, medium, and low priority through the horizon scanning process;
- consider the recommended committee workplan for 2024/2025 in Annex D;
- consider whether advice from additional external advisors would help in achieving the work recommendations;
- consider the frequency of review for treatment add-ons (see section 7 below).

7. Frequency of review for treatment add-ons

7.1. The literature review for the treatment add-ons that are on HFEA website is carried out separately to the annual horizon scanning process. Since inception of HFEA's rating system for treatment add-ons in 2017, the ratings have only changed twice:

- October 2019 - PGT-A rating went from amber to red due to published research
- October 2023 – The rating system was changed from RAG ratings to 5-point ratings

7.2. This suggests that good quality, significant research on treatment add-ons, which impact upon the rating of the add-on, is published infrequently.

7.3. Considering this, and the resources required to carry out a separate literature review specifically for treatment add-ons, the Executive recommends that the review of the evidence base and ratings for treatment add-ons is performed every three or five years. Between reviews, the Committee and the Executive should continue to actively monitor and highlight relevant publications that could change the rating of an add-on, and an ad-hoc review can be carried out for a particular add-on should this arise.

8. Annex A: Briefings on key issues identified during horizon scanning

The briefings below have been written on two of the proposed high priority topics to highlight significant advancements ahead of when the topics are next scheduled to be discussed, as per the committee workplan (Annex D).

Testicular tissue transplantation to restore fertility in males

Background

8.1. The development and implementation of strategies to preserve future fertility for prepubertal males who have received chemotherapy, radiotherapy or other gonadotoxic therapies are of critical importance. Cryopreservation of immature testicular tissue obtained following biopsy is increasingly being used to preserve spermatogonial stem cells. The frozen-thawed tissue can then be used for re-transplantation back to the patient when they reach adulthood, in the hope it could generate functional sperm (Goossens et al., 2020; Mitchell & Ives, 2023).

8.2. The clinical aspects of this topic were reviewed by an invited speaker at the October 2023 SCAAC meeting, during the discussion on the topic of 'in vitro derived gametes'. During this discussion, it was noted that there are at least three centres worldwide (UK, USA and Belgium) which have obtained, or are in the process of obtaining, ethical approval to transplant the cryopreserved tissues back to the patients as clinical treatment.

8.3. The cryopreservation of testicular tissue is an authorised process. The HFEA and Human Tissue Authority (HTA) have issued a joint statement on ovarian and testicular tissue storage. Establishments storing tissue containing immature gametes require a licence from both the HFEA and the HTA if the tissue containing the gametes is being stored for future transplant into a recipient, or where the intended future use of the tissue is unknown.

Summary of developments

8.4. Cryopreservation of immature testicular tissue is being offered by increasing numbers of centers throughout the world (Anderson et al., 2015; Braye et al., 2019; Goossens et al., 2020; Valli-Pulaski et al., 2019). Additionally, several international networks have been established to focus on this topic, including ORCHID-NET, Nordfertil, and a coordinated network of academic centers (Valli-Pulaski et al., 2019). Establishment of these networks demonstrates increased efforts to offer fertility preservation strategies to young boys.

8.5. A feasibility study in primates demonstrated the successful use of this technique to result in functional sperm production and live offspring (Fayomi et al., 2019). Although the production of functional sperm through the re-implantation of testicular tissue is yet to be demonstrated in humans, it is expected that clinical trials on this are imminent.

Level of work recommendation

8.6. The Committee will be asked to monitor any further developments in the scientific and clinical literature relating to testicular tissue transplantation to restore fertility in males as part of the committee's workplan. It is proposed that this topic be discussed by the committee in October

2025, which will be two years after introduction. The Executive will continue to monitor any developments as part of the annual horizon scanning.

Emerging technologies in embryo and gamete testing

Background

8.7. The Executive recommends that 'metabolomic profiling' is incorporated into the topic of 'emerging technologies in embryo and gamete testing'. This sub-topic was identified at HFEA's horizon scanning meeting held during the European Society for Human Reproduction and Embryology (ESHRE) annual conference in 2023.

8.8. An invited speaker at this meeting described how metabolomic profiling has the scope to become an adjunct tool to embryo assessment for prediction of embryo implantation potential. However, the speaker noted that results from metabolomic profiling have a large dependency on the culture media used. Furthermore, the timeline for commercialisation of metabolomic applications is long, given safety of such technology has to be proven before bringing it to market. The speaker highlighted key challenges with metabolomic profiling related to finding technology-driven ways of using these techniques more effectively and improving the technology used. It was further discussed that while these issues are complex, metabolomic profiling does not raise a unique regulatory challenge, especially if it is only used as an assessment or quality control in the laboratory.

8.9. Dynamic nutrient requirements during pre-implantation embryo development are essential to support the energetic and biosynthetic needs of early embryos (Zhao et al., 2023). The increase in number of functional metabolites being identified during each stage of early embryo development has led to a proposed concept of a new class of 'developmental metabolites' (Zhao et al., 2023). It has been hypothesised that they may play an important role not only in metabolism but also in regulating development. The criteria to define such metabolites are:

- metabolites should be specifically present at a certain stage or in a specific type of cell during early embryo development, while rarely present during other physiological contexts; or metabolites may be more broadly present but should exhibit a specific function related to development at a specific time.
- metabolites should be involved in regulating development through a clearly defined mechanism or process.

8.10. A summary of the relevant literature between January and December 2023 is provided below.

Summary of developments

8.11. A study by (Xu et al., 2023) used metabolome and transcriptome analysis to evaluate the global metabolomic profiles of follicular fluid from women with polycystic ovarian syndrome (PCOS). The authors demonstrated that PCOS women exhibited distinct metabolic features in follicles, such as the increase in fatty acid utilization and the downregulation in amino acid metabolism. A review by (Minasi et al., 2023) provides an overview of different approached to evaluate oocyte quality and competence including metabolomic analysis of spent culture medium.

8.12. A study by (Martínez-Moro et al., 2023) performed metabolomics analysis on cumulus cells (CC) from cumulus–oocyte complexes (COCs) of IVF/ICSI cycles with known reproductive outcome. The abundance of malonate, 5-oxyproline, and erythronate in CC was significantly

higher in COCs ultimately established a pregnancy, providing clues on the pathways required for oocyte competence.

8.13. A study by (Liang et al., 2023) combined metabolomic profiling of spent embryo culture medium and clinical variables to create an implantation prediction model as an adjunct to morphological screening of day 3 embryos (42 embryos from 34 IVF patients) with an accuracy of 0.88. Similarly, (Cheredath et al., 2023) used metabolomic data from spend culture medium and embryological data of day 5 blastocysts (from 56 infertile couple undergoing ICSI) to develop custom artificial neural network model for prediction of embryo implantation potential.

8.14. (Liu et al., 2023) performed a targeted metabolomics study in plasma from early embryonic development arrest (EEDA) patients (n = 27) and normal pregnant women (NPW, n = 27) to identify potential diagnostic marker metabolites. The authors suggest that S-methyl-5'-thioadenosine, kynurenine, leucine, and malate could be used as a panel of metabolites for EEDA diagnosis, with area under the curve (AUC) of 0.941.

8.15. A study by (Molina et al., 2023) analysed receptive-phase endometrial metabolome profiles among women from couples with infertility of different aetiology and the associations of these profiles with Mediterranean diet (MD). The authors found lower levels of polyunsaturated fatty acids in women with endometriosis and recurrent implantation failure compared to those with no clear endometrial alterations. Moreover, MD adherence seemed to be associated with the endometrial metabolomic profile in a manner dependent on the health status of the uterus.

Level of work recommendation

8.16. The Executive will continue to monitor any developments as part of the annual horizon scanning.

9. References

Anderson, R. A., Mitchell, R. T., Kelsey, T. W., Spears, N., Telfer, E. E., & Wallace, W. H. B. (2015). Cancer treatment and gonadal function: experimental and established strategies for fertility preservation in children and young adults. *The Lancet Diabetes & Endocrinology*, *3*(7), 556–567. https://doi.org/10.1016/S2213-8587(15)00039-X

Braye, A., Tournaye, H., & Goossens, E. (2019). Setting Up a Cryopreservation Programme for Immature Testicular Tissue: Lessons Learned After More Than 15 Years of Experience. *Clinical Medicine Insights: Reproductive Health*, *13*, 117955811988634. https://doi.org/10.1177/1179558119886342

Cheredath, A., Uppangala, S., Asha, C. S., Jijo, A., Vani Lakshmi, R., Kumar, P., Joseph, D., Nagana, N. G., Kalthur, G., & Adiga, S. K. (2023). Combining Machine Learning with Metabolomic and Embryologic Data Improves Embryo Implantation Prediction. *Reproductive Sciences*, *30*(3), 984–994. https://doi.org/10.1007/s43032-022-01071-1

Fayomi, A. P., Peters, K., Sukhwani, M., Valli-Pulaski, H., Shetty, G., Meistrich, M. L., Houser, L., Robertson, N., Roberts, V., Ramsey, C., Hanna, C., Hennebold, J. D., Dobrinski, I., & Orwig, K. E. (2019). Autologous grafting of cryopreserved prepubertal rhesus testis produces sperm and offspring. *Science (New York, N.Y.)*, *363*(6433), 1314–1319. https://doi.org/10.1126/SCIENCE.AAV2914

Goossens, E., Jahnukainen, K., Mitchell, R. T., Van Pelt, A. M. M., Pennings, G., Rives, N., Poels, J., Wyns, C., Lane, S., Rodriguez-Wallberg, K. A., Rives, A., Valli-Pulaski, H., Steimer, S., Kliesch, S., Braye, A., Andres, M. M., Medrano, J., Ramos, L., Kristensen, S. G., … Stukenborg, J. B. (2020).

Fertility preservation in boys: Recent developments and new insights †. *Human Reproduction Open*, *2020*(3). https://doi.org/10.1093/hropen/hoaa016

Liang, R., Duan, S. N., Fu, M., Chen, Y. N., Wang, P., Fan, Y., Meng, S., Chen, X., & Shi, C. (2023). Prediction model for day 3 embryo implantation potential based on metabolites in spent embryo culture medium. *BMC Pregnancy and Childbirth*, *23*(1), 425. https://doi.org/10.1186/s12884-023-05666-7

Liu, Y., Fan, X., Pang, H., Liu, S., Wang, B., Wang, C., Yan, Q., Song, W., Hu, Z., Liu, Q., & Shi, Y. (2023). Metabolomics Identifies a Panel of Diagnostic Biomarkers for Early Human Embryonic Development Arrest. *Journal of Proteome Research*, *22*(4), 1280–1286. https://doi.org/10.1021/acs.jproteome.2c00816

Martínez-Moro, Á., González-Brusi, L., Querejeta-Fernández, A., Padilla-Ruiz, E., García-Blanco, J., & Bermejo-Álvarez, P. (2023). Metabolomics analysis of human cumulus cells obtained from cumulus–oocyte complexes with different developmental potential. *Human Reproduction*, *38*(11), 2187–2195. https://doi.org/10.1093/humrep/dead181

Minasi, M. G., Anagnostopoulou, C., Boitrelle, F., Vogiatzi, P., Sallam, H., Saleh, R., Colpi, G., & Agarwal, A. (2023). Oocytes evaluation and in-vitro fertilization/ intra cytoplasmic sperm injection outcomes. *Panminerva Medica*, *65*(2), 179–187. https://doi.org/10.23736/S0031-0808.23.04838-3

Mitchell, R. T., & Ives, J. (2023). Testicular tissue re-implantation and the 'hostile testis.' *Human Reproduction*. https://doi.org/10.1093/humrep/dead258

Molina, N. M., Jurado-Fasoli, L., Sola-Leyva, A., Sevilla-Lorente, R., Canha-Gouveia, A., Ruiz-Durán, S., Fontes, J., Aguilera, C. M., & Altmäe, S. (2023). Endometrial whole metabolome profile at the receptive phase: influence of Mediterranean Diet and infertility. *Frontiers in Endocrinology*, *14*, 1120988. https://doi.org/10.3389/fendo.2023.1120988

Valli-Pulaski, H., Peters, K. A., Gassei, K., Steimer, S. R., Sukhwani, M., Hermann, B. P., Dwomor, L., David, S., Fayomi, A. P., Munyoki, S. K., Chu, T., Chaudhry, R., Cannon, G. M., Fox, P. J., Jaffe, T. M., Sanfilippo, J. S., Menke, M. N., Lunenfeld, E., Abofoul-Azab, M., … Orwig, K. E. (2019). Testicular tissue cryopreservation: 8 years of experience from a coordinated network of academic centers. *Human Reproduction*, *34*(6), 966–977. https://doi.org/10.1093/humrep/dez043

Xu, Y., Zhou, Z., Zhang, G., Yang, Z., Shi, Y., Jiang, Z., Liu, Y., Chen, H., Huang, H., Zhang, Y., & Pan, J. (2023). Metabolome implies increased fatty acid utilization and histone methylation in the follicles from hyperandrogenic PCOS women. *The Journal of Nutritional Biochemistry*, *125*, 109548. https://doi.org/10.1016/j.jnutbio.2023.109548

Zhao, J., Wang, W., Zhang, L., Zhang, J., Sturmey, R., & Zhang, J. (2023). Dynamic metabolism during early mammalian embryogenesis. In *Development (Cambridge)* (Vol. 150, Issue 20). Company of Biologists Ltd. https://doi.org/10.1242/dev.202148

10. Annex B: Spreadsheet of papers identified through horizon scanning

This document was shared with members as a separate document in spreadsheet format.

11. Annex C: Topic prioritisation table

The table below details the decisions that were made by the Executive in consideration of topic prioritisation.

Topic	Is it within HFEA remit?	Is timescale for likely clinical introduction now or within 3 years?	Would there be high patient demand/clinical use if it were introduced?	Is it technically feasible?	Are there ethical issues or public interest raised?	Rating considered by Executive
Alternative methods to derive embryonic and embryonic-like stem cells	Yes	No	No	Yes	Yes	High
Artificial intelligence (AI), robotics and automation in fertility treatment	Yes	Yes	Yes	Yes	Yes	High
Emerging technologies in embryo and gamete testing	Yes	Yes	Yes	Yes	Yes	High
Germline genome editing	Yes	No	No	Yes	Yes	High
Impact of long-term cryopreservation of gametes and embryo	Yes	Yes	Yes	Yes	Yes	High
In vitro derived gametes	Yes	No	Yes	Yes	Yes	High
Scientific considerations relevant to the '14-day rule'	Yes	N/A	N/A	Yes	Yes	High
Stem cell based embryo models	No	No	No	Yes	Yes	High
Testicular tissue transplantation to restore fertility in males	Yes	Yes	No	Yes	No	High
Health outcomes in children conceived by ART (including the impact of culture media)	No	Yes	Yes	Yes	Yes	Medium
Impact of the microbiome on fertility and fertility treatment outcomes	No	Yes	Yes	Yes	Yes	Medium
Mitochondrial donation	Yes	Yes	No	Yes	Yes	Medium (see 4.1)
Artificial wombs for early or whole gestation (ectogenesis)	No	No	No	No	Yes	Low
Impact of stress on fertility treatment outcomes	No	N/A	N/A	N/A	Yes	Low

12. Annex D: Committee workplan 2024-2025

Priority topic	Item to be presented	Possible speaker	Last discussed	Next discuss
Emerging technologies in embryo and gamete testing	Literature review	Internal	Oct-21	Jun-24
Impact of stress on fertility treatment outcomes	Literature review	Internal	Jun-22	Jun-24
Alternative methods to derive embryonic and embryonic-like stem cells	Literature review	Internal	Jan-22	Jun-24
Scientific considerations relevant to the '14-day rule' (input may be requested by the Authority as part of Act reform work)	Literature review	Internal	Oct-22	Oct-24
Stem cell based embryo models	Literature review	Internal/SCAAC member	Feb-23	Oct-24
Mitochondrial donation	Programme update	Newcastle Fertility Centre	Jul-23	Oct-24
Artificial wombs for early or whole gestation (ectogenesis)	Literature review	Academic	Added Jan-22	Feb-25
Health outcomes in children conceived by ART (including the impact of culture media)	Literature review	Internal	Oct-23	Feb-25
In vitro derived gametes	Literature review	Internal	Oct-23	Feb-25
Impact of the microbiome on fertility and fertility treatment outcomes	Literature review	Academic	Oct-23	Jun-25
Artificial intelligence (AI), robotics and automation in fertility treatment	Literature review	Internal	Feb-24	Jun-25
Germline genome editing	Literature review	Academic	Feb-24	Jun-25
Impact of long-term cryopreservation of gametes and embryo	Literature review	Internal	Feb-24	Jun-25

13. Annex E: Committee purpose and function as per HFEA standing orders

13.1. To support the committee's discussion about their planned activity for 2024/25, the Executive would like to remind members of the purpose and function of the Committee, as detailed in section 5 of the HFEA standing orders.

13.2. Section 5.1 of Annex A states that the purpose of the Committee "is to advise the Authority on scientific and clinical developments (including research) in assisted conception, embryo research and related areas."

13.3. Section 5.2 of Annex A states the function of the Committee shall be to:

- make recommendations to the Authority on the safety and efficacy of scientific and clinical developments (including research) in assisted conception, embryo research and related areas;
- make recommendations to the Authority on patient information relating to those scientific and clinical developments;
- advise the Authority on significant implications for licensing and regulation arising out of such developments, and;

- where required, work with the Authority members to consider the social, ethical and legal implications arising out of such developments.

The impact of long-term cryopreservation of gametes and embryos

Details about this paper

Area(s) of strategy this paper relates to:	Shaping the future and the best care
Meeting:	Scientific and Clinical Advances Advisory Committee (SCAAC)
Agenda item:	7
Paper number:	HFEA (05/02/2024) 007
Meeting date:	05 February 2024
Author:	Molly Davies, Scientific Policy Officer (HFEA)
Annexes	None

Output from this paper

For information or advice?	For information
Recommendation:	Members are asked to: • advise the executive if they are aware of any other recent developments; • consider the progress of research into the impact of long-term cryopreservation on gametes and embryos; and • review whether any outputs from the HFEA are required.
Resource implications:	N/A
Implementation date:	N/A
Communication(s):	N/A
Organisational risk:	Low

1. Introduction

1.1. From 1 July 2022, amendments to the Human Fertilisation and Embryology (HFE) Act 1990 came into force, permitting the storage of eggs, sperm and/or embryos for use in their own treatment or for donation to another person's treatment to be stored for up to 55 years.

1.2. The impact of long-term cryopreservation was introduced as a new high-priority topic for consideration by the SCAAC during the February 2023 meeting. This followed the concern that the change in the law in 2022 to enable storage for up to 55 years may increase the number of gametes and embryos in long-term storage and thus it was considered pertinent for the SCAAC to monitor any safety or viability concerns relating to the keeping of gametes or embryos in long-term storage.

1.3. The HFEA's most recent Fertility trends shows that egg storage cycles increased from 373 cycles in 2011 to 4,215 cycles in 2021, while embryo storage cycles increased from 230 cycles to 10,719 cycles. Additionally, frozen embryo transfer (FET) cycles have increased in use, with a 41% increase in FET cycles being seen between 2017 and 2021.

1.4. This paper presents novel research on the impact of long-term cryopreservation of gamete and embryos primarily published between 12 December 2022 and 22 January 2024[1]. Ethical and practical considerations relevant to the topic are summarised.

1.5. The Executive notes that the current paper provides a summary of the results of publications identified in the specified time frame of when literature search was performed. Therefore, this paper provides a summary of the findings described in published studies and not an assessment of study validity.

2. Research

Clinical outcomes

2.1. A retrospective cohort study conducted by Zheng et al., 2022, investigated the impact of cryopreservation duration on pregnancy outcomes following 6,327 cycles of vitrified-warmed autologous blastocyst transfers. Blastocysts were divided into six groups depending on duration of storage (<10 years). Implantation rate, chances of biochemical pregnancy, clinical pregnancy, ongoing pregnancy, and live birth were found to significantly decrease as storage duration increased up to 25 months. Subgroup analysis confirmed progression of declining pregnancy outcomes as storage duration increased, particularly where material was stored for over 72 months (n=72), suggesting that long-term storage of embryos may negatively impact pregnancy outcomes.

2.2. A retrospective cohort study by Yan et al., 2022 looked at effects of long-term vitrification on pregnancy outcomes. Patients were grouped according to duration of storage (in years): group

[1] For completeness, studies which were not identified during the previous literature search performed in **February 2023** have been included in this paper.

1, <3 (n = 1,890), group 2, 3-4 (n = 2,693), group 3, 4-5 (n = 1,344), group 4, 5-6 (n = 578), and group 5, ≥ 6 years but ≤ 10.5 years (n = 395). Rates of biochemical pregnancy, clinical pregnancy, and live birth were significantly decreased when blastocysts were stored for more than 6 years (group 5) compared with those stored for less than 3 years (group 1), with no distinct differences found among groups 1, 2, 3, and group 4. No significant differences were found in rates of miscarriage, ectopic pregnancy or neonatal outcomes between groups. In addition, survival rates of vitrified blastocysts significantly decreased with prolonged storage.

2.3. By contrast, the retrospective bi-centre study conducted by X. Li et al., 2023, reported unimpaired pregnancy and neonatal outcomes following the transfer of embryos vitrified for up to 7 years. No significant differences were observed in biochemical pregnancy rate, implantation rate, clinical pregnancy rate (CPR), ongoing pregnancy rate or live birth rate (LBR) in subgroups of women undergoing FET with storage durations of 1-6 months (n=612), 7-12 months (n=202), 13-36 months (n=141), and 37-84 months (n=76). In addition, no significant impact was found on neonatal outcomes.

2.4. The impact of storage time on pregnancy and neonatal outcomes following vitrified-warmed blastocyst transfer was further analysed by (Ma *et al.*, 2023) in their retrospective cohort study. Patients were divided into five groups: group A, storage time <3 months (n =1621), group B, storage time of between 4-6 months (n = 657), group C, storage time of 7-12 months (n = 225), group D, storage time of 13-24 months (n = 104), and group E, storage time of 25-98 months (n = 331). After adjusting for confounding factors, results showed that there were no significant differences in live birth rate, β-human chorionic gonadotropin (hCG) - positive rate, CPR and miscarriage rate between Group A and the other groups. Moreover, no significant differences were found between neonatal outcomes of each group.

2.5. He et al., 2023 performed a single-centre, retrospective analysis of 426 FET cycles which followed storage of embryos by vitrification for up to 6 years. Preferentially matched participants were divided into three groups according to storage time: group A (>72 months), group B (0-3 months, matched according to the age at oocyte retrieval) and group C (0-3 months, matched according to age at embryo transfer). No significant differences in hCG - positive rate, CPR, miscarriage rate, LBR and neonatal outcomes between the groups, providing further evidence that long-term cryopreservation of embryos had no effect on the pregnancy and neonatal outcomes. The above results show consistency with earlier research looking at perinatal outcomes following the long-term storage of blastocysts with equal grades. Lin et al., 2021, performed a retrospective study analysing 7579 FET cycles which had been allocated four grades of quality and separated into categories by duration of storage (>5). For blastocysts with the same grade, the length of storage time had no statistical effect on blastocyst survival rate, CPR/implantation rate, LBR, and abortion rate. As similar neonatal outcomes were obtained over time, authors concluded that cryopreservation time does not negatively affect perinatal outcomes of vitrified-thawed blastocysts of equal quality.

2.6. J. Li et al., 2020, also offer evidence for the safety of using long-stored embryos after vitrification in their 2020 retrospective study. A total of 24,698 patients who had undergone FET were grouped according to storage time: group 1, <3 months (n = 11,330), group 2, storage between 3-6 months (n = 9,641), group 3, storage between 6-12 months (n = 3,188), and group 4, storage between 12 and 24 months (n = 566). Whilst the chance of biochemical pregnancy was found to significantly decrease with increasing storage time, the relationship between miscarriage, ectopic

pregnancy and storage time showed no statistical significance. No evidence of differences in adverse neonatal outcomes, including preterm birth, low birthweight, high birthweight, macrosomia or birth defects, was reported.

2.7. Mao et al., 2022 evaluated the impact of the duration of cryopreservation of vitrified-thawed embryos across 31,143 patients, considering embryos stored for >731 days. Alongside a reduction seen in embryo survival rate, prolonged storage time was also found to negatively affect CPR. No significant differences were found in neonatal health outcomes, offering evidence for the safety of using vitrified embryos stored for long durations.

2.8. The impact of prolonged storage time on post thaw survival rates was also noted in the retrospective analysis study conducted by Castravet et al., 2023. This study used a retrospective analysis of 156 cycles of fertility treatment using vitrified-thawed donated oocytes to determine outcomes. Cycles were placed into 5 groups according to length of storage time: group 1, <3 months (n = 25), group 2, 3-6 months (n = 32), group 3, 3-6 months (n = 39), group 4, 12-24 months (n = 38), and group 5, >24 months (n = 22). Authors recorded that prolonged storage time of vitrified oocytes had an effect on the post-thaw survival rates. However, when adjusted for cofounders, relationships between fertilization rate or clinical outcomes and oocyte storage time were not found to be significant.

2.9. Torra-Massana et al., 2023 investigated the impact of long-term storage of donated oocytes (n = 41,783) on the laboratory and reproductive outcomes following ICSI treatment according to five categories of storage time (in years): ≤1(reference group), 1-2, 2-3, 3-4 and >4. After adjusting for confounders, mean oocyte survival was not found to significantly decrease with longer storage time, with no significant effect of storage time on fertilisation rate being recorded. In addition, reproductive outcomes were comparable across storage times, with longer-term storage (>4 years) not found to affect the chances of clinical pregnancy or LBR.

2.10. Azambuja et al., 2023, presented a novel case report on the outcome of ICSI treatment following 13 years of oocyte cryopreservation using a slow, chlorine-based cryopreservation method. Authors documented the successful live birth of a healthy boy following a 38-week singleton pregnancy, demonstrating the efficacy of slow-freeze techniques when preserving the viability and quality of oocytes.

2.11. A further case study presented by Tsakos et al., 2023 reported the delivery of a healthy child via gestational surrogacy following the transfer of an embryo cryopreserved via slow-freeze for a duration of 10-years. Follow up at 20 months demonstrated normal physical and cognitive development of the child.

Transcriptome Analysis

2.12. Li et al., 2022, compared the expression profiles of messenger RNA (mRNA) and long non-coding RNA (lncRNA) across three groups of fresh (n=3) and vitrified-warmed human embryos, stored for 3- (n=4) and 8- (n=4) years. No differentially expressed mRNA or lncRNAs were identified between the 3- and 8- year groups, however a total of 128 mRNAs and 365 long-coding RNAs were differentially expressed between the vitrified-warmed embryos when compared to the fresh embryos. Authors hypothesised that differential expression of vitrified-warmed embryos resulted from damage incurred during the warming procedure, concluding that the finding of a stable transcriptome indicating that long-term cryopreservation does not affect human embryos at the

single cell level. Further research is required to verify whether long-term cryopreservation has an impact on other molecular mechanisms, such as epigenetic modification.

2.13. Huang et al., 2024, analysed the impact of the duration of cryopreservation on the expression of microRNAs on freeze-thawed semen stored for up to 15 years. microRNA expression profiling revealed that differential expression of microRNAs between fresh and cryopreserved samples became more pronounced as duration of storage increased, indicating that the microRNA expression profile may be modified by extensions to storage duration.

Genetic analysis

2.14. Zhu et al., 2023 investigated whether storage time has an impact on the DNA methylation profiles of human embryos. Using single-cell whole-genome bisulfite sequencing the study compared the methylation patterns between fresh embryos (n = 3) and those cryopreserved through vitrification for 3 (n = 3) and 8 years (n = 3) respectively. When compared to the fresh group, a total of 587 differentially methylated regions (DMR) in the 3-year group and 540 DMRs in the 8-year group were identified. As the distribution of DMRs was found to similar between groups, Authors concluded that long-term cryopreservation does not affect the DNA methylation profiles of vitrified-warmed human embryos at the single-cell level.

Future Research using the HFEA Register

2.15. Recently the HFEA's Register Research Panel approved an h application to investigate this topic using data held on the HFEA Register. The research study, led by researchers at the University of Aberdeen, aims to investigate the impact of the duration of freezing of IVF embryos on pregnancy and perinatal outcomes through analysis of the HFEA's Register data. Outcomes will be measured by LBR, gestational age at birth, birthweight at delivery, birthweight adjusted for gestational age and gender, and presence of congenital anomalies. Further information will shortly be available on the HFEA's data research webpage.

3. Usage rate of frozen gametes

3.1. Previous research has highlighted that only a minority of male patients banking their semen prior to undergoing treatment for cancer subsequently retuned to use their frozen samples. In 2021,Ferrari et al., 2021 reviewed the usage rate for these patients, reporting that of 1524 patients with at least one cryopreserved sperm sample (median time 12 years, interquartile range: 7-16 years) only 9.4% (n = 144) had returned to use their samples for treatment, indicating that usage rate of frozen gametes in this patient group remains low, even with the extended duration of storage.

3.2. A similarly low return rate was reported by Immediata et al., 2022 who considered female patients who had previously preserved their oocytes prior to cancer treatment. Of the 142 patients followed up in the study, only 11.7% (n = 20) returned for treatment. Reasons as to why patients did not return for treatment were explored by the study.

3.3. Yang et al., 2022investigated usage rates for patients who had elected to undergo cryopreservation for non-medical reasons. After the storage duration exceeded ten years, the probabilities of thawing oocytes were 10.6%, 26.6%, and 12.7% from women who cryopreserved their oocytes at the age ≤ 35 years, 36-39 years, and ≥ 40 years, respectively. Indicating that

return rates after a longer duration of storage are relatively low for patients undergoing long-term elective cryopreservation.

3.4. A study by Blakemore et al., 2021 assessed the outcomes of planned oocyte cryopreservation and presented limited data on the mean time of cryopreservation for patients freezing oocytes by age of freezing. Although not the primary outcome of this study, authors concluded that in the small cohort the duration of cryopreservation did not predict live birth.

3.5. In their review article, Go et al., 2022 discuss the challenge of unclaimed cryopreserved embryos resulting from long-term storage, highlighting its impact on clinic and laboratory operations as well as solutions and strategies that can be offered to patients to manage decisions about cryopreserved embryos.

4. Conclusions

4.1. Research in this area continues to be limited by reduced cohorts of patients storing gametes or embryos for longer durations and the observational nature of the current studies. As the limit on storage in the UK (55-years) greatly exceeds that of the cohorts studied, at present it is not possible to draw conclusions on how long-term storage may affect clinical outcomes for patients in the far future.

5. Recommendations

5.1. Members are asked to:

- advise the Executive if they are aware of any other recent developments;
- consider the progress of research into the impact of long-term cryopreservation on gametes and embryos; and
- review whether any outputs from the HFEA are required.

6. References

Azambuja R, Badalotti M, Okada L, Cortes LS, Hentschke MR, Petracco A. Fertility preservation: a case report of a newborn following 13 years of oocyte cryopreservation. *JBRA Assist Reprod* [Internet] 2023;**27**:328–331. Brazil.

Blakemore JK, Grifo JA, Devore SM, Hodes-Wertz B, Berkeley AS. Planned oocyte cryopreservation-10-15-year follow-up: return rates and cycle outcomesAvailable from: https://doi.org/10.1016/j.fertnstert.2021.01.011.

Castravet I, Barry F, Gala A, Ferrières-Hoa A, Loup V, Mullet T, Brunet C, Brouillet S, Hamamah S. Impact de la durée de cryoconservation ovocytaire dans le cadre du don d'ovocytes sur le taux de succès clinique. *Gynécologie Obstétrique Fertilité & Sénologie* 2023;**51**:206–211. Elsevier Masson.

Ferrari S, Paffoni A, Reschini M, Noli S, Dallagiovanna C, Guarneri C, Filippi F, Somigliana E. Variables affecting long-term usage rate of sperm samples cryopreserved for fertility preservation in cancer patients. *Andrology* [Internet] 2021;**9**:204–211. John Wiley & Sons, Ltd.

Go KJ, Romanski PA, Bortoletto P, Patel JC, Srouji SS, Ginsburg ES. Meeting the challenge of unclaimed cryopreserved embryos. *Fertil Steril* [Internet] 2022;**119**:15–20. United States.

He H, Jiang R, Ren X, Jin L, Jiang Y. The safety of human embryos following long-term cryopreservation (>6 years) on vitrification. *Cryo Letters* [Internet] 2023;**44**:178–184. England.

Huang C, Ji X-R, Huang Z-H, Liu Q, Wang R-J, Fan L-Q, Wu H-L, Bo H, Zhu W-B. Long-term storage modifies the microRNA expression profile of cryopreserved human semen. *Biomol Biomed* [Internet] 2024;**24**:51–60. Bosnia and Herzegovina.

Immediata V, Cirillo F, Baggiani A, Zanagnolo MF, Ronchetti C, Morenghi E, Cesana A, Specchia C, Levi-Setti PE. Why are they not coming back? A single-center follow-up study on oncological women oocyte's storing for fertility preservation. *Front Endocrinol (Lausanne)* [Internet] 2022;**13**:. Frontiers Media SA.

Li J, Yin M, Wang B, Lin J, Chen Q, Wang N, Lyu Q, Wang Y, Kuang Y, Zhu Q. The effect of storage time after vitrification on pregnancy and neonatal outcomes among 24 698 patients following the first embryo transfer cycles. *Hum Reprod* [Internet] 2020;**35**:1675–1684. Hum Reprod.

Li J, Zhu L, Huang J, Liu W, Han W, Huang G. Long-Term Storage Does Not Affect the Expression Profiles of mRNA and Long Non-Coding RNA in Vitrified-Warmed Human Embryos. *Front Genet* [Internet] 2022;**12**:751467. Switzerland.

Li X, Guo P, Blockeel C, Li X, Deng L, Yang J, Li C, Lin M, Wu H, Cai G, *et al.* Storage duration of vitrified embryos does not affect pregnancy and neonatal outcomes after frozen-thawed embryo transfer. *Front Endocrinol (Lausanne)* [Internet] 2023;**14**:1148411. Switzerland.

Lin R, Zhou H, Wang C, Chen H, Shu J, Gan X, Xu K, Zhao X. Does longer storage of blastocysts with equal grades in a cryopreserved state affect the perinatal outcomes? *Cryobiology* 2021;**103**:87–91. Academic Press.

Ma Y, Sun M, Wen T, Ding C, Liu LW, Meng T, Song J, Hou X, Mai Q, Xu Y. Storage time does not influence pregnancy and neonatal outcomes for first single vitrified high-quality blastocyst transfer cycle. *Reprod Biomed Online* [Internet] 2023;**47**:. Elsevier Ltd.

Mao Y, Tang N, Luo Y, Yin P, Li L. Effects of vitrified cryopreservation duration on IVF and neonatal outcomes. *J Ovarian Res* [Internet] 2022;**15**:1–10. BioMed Central Ltd.

Torra-Massana M, Miguel-Escalada I, Vassena R, Rodríguez A. Long-term storage of vitrified oocytes does not affect pregnancy and live birth rates: analysis of 5362 oocyte donation cycles. *Reprod Biomed Online* [Internet] 2023;**47**:103228. Netherlands.

Tsakos E, Xydias EM, Ziogas AC, Tsagias N, Pappa K, Stergioula A, Bimpa K. Delivery of a Healthy Child Through International Gestational Surrogacy 10 Years Following Female Fertility Preservation and In Vitro Fertilization (IVF) for Recurrent Breast Cancer: A Case Report. *Cureus* [Internet] 2023;**15**:e43827. United States.

Yan Y, Zhang Q, Yang L, Zhou W, Ni T, Yan J. Pregnancy and neonatal outcomes after long-term vitrification of blastocysts among 6,900 patients after their last live birth. *Fertil Steril* [Internet] 2022;**119**:36–44. United States.

Yang IJ, Wu MY, Chao KH, Wei SY, Tsai YY, Huang TC, Chen MJ, Chen SU. Usage and cost-effectiveness of elective oocyte freezing: a retrospective observational study. *Reprod Biol Endocrinol* [Internet] 2022;**20**:123. BMC.

Zheng Q, Mo M, Zhang H, Xu S, Xu F, Wang S, Zeng Y. Prolong cryopreservation duration negatively affects pregnancy outcomes of vitrified-warmed blastocyst transfers using an open-device system: A retrospective cohort study. *Eur J Obstet Gynecol Reprod Biol* [Internet] 2022;**281**:68–75. Ireland.

Zhu L, Sun L, Liu W, Han W, Huang G, Li J. Long-term storage does not affect the DNA methylation profiles of vitrified-warmed human embryos. *Mol Reprod Dev* [Internet] 2023; United StatesAvailable from: http://dx.doi.org/10.1002/mrd.23713.

Genome editing

Details about this paper

Area(s) of strategy:	Shaping the future
Meeting:	Scientific and Clinical Advances Advisory Committee (SCAAC)
Agenda item:	08
Paper number:	HFEA (05/02/2024) 008
Meeting date:	05 February 2024
Author:	Ana Hallgarten, Emerging Technologies Team Lead (DHSC) (former HFEA Public Policy Manager)
Annexes	None

Output from this paper

For information or advice?	For recommendation
Recommendation:	Members are asked to: • advise the executive if they are aware of any other recent developments; • discuss the potential for clinical application of this technology and identify particular concerns or issues that should be highlighted; and • review whether any outputs from the HFEA are required.
Resource implications:	N/A
Implementation date:	Recommendations will be implemented as soon as feasible
Communication(s):	To be determined
Organisational risk:	Low

1. Introduction

1.1. The HFE Act does not permit interventions in the nuclear DNA of gametes or zygotes for the purposes of germline genome editing in reproduction. Genetically modified embryos are currently only permitted in research and cannot be grown in culture for more than 14 days. Furthermore, embryo research can only be carried out under licence from the HFEA and must include Research Ethics Committee approval.

1.2. Genome editing research using human gametes and embryos has already improved our understanding of gene function, early human development, DNA-repair mechanisms, and genomic rearrangements (mutations such as deletions that change the gene content of a genome or the arrangement of the genes on a genome). Genome editing techniques can be used to study the relationship between genes and diseases, and to explore the possibility of disease prevention or treatment.

1.3. Genome editing can be used to induce changes in cells of the germline (gametes or their precursors, or early embryos) that can be non-heritable if no pregnancy is established (i.e. research in vitro) or heritable if the embryos are allowed to develop in utero. The methods can also be used to make non-heritable changes in somatic cells. While the HFEA regulates research with genome editing in human embryos and admixed embryos, it does not regulate somatic genome editing applications, such as gene therapy.

1.4. Arguably the greatest advance in both heritable and non-heritable genome editing has been the development of the CRISPR-Cas9 system or related methods. CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeats. In genome editing, CRISPR/Cas9 can be used to make a double-strand break in DNA that is usually repaired by the non-homology end-joining (NHEJ) mechanism active in cells. This tends to lead to the formation of indels, small insertions or deletions, and is an efficient way to make mutations in genes. However, it can also cause larger deletions, insertions, translocations, or gene conversion events that can result in loss of heterozygosity, and thus can lead to deleterious consequences.

1.5. Two CRISPR RNA guides can be used together with a DNA template to replace one DNA sequence with another. This makes use of homology directed repair (HDR) mechanisms. However, this mechanism appears to be less effective than NHEJ, and there is still a risk that unwanted consequences occurring with NHEJ may also be present with HDR.

1.6. More recently, advances have been made in methods that avoid creating double stranded breaks. These include base editing and prime editing methods which may be more appropriate for making germline and heritable changes.

1.7. Although there is a focus on the use of these technologies to modify nuclear DNA, genome editing techniques can also be applied to modify mitochondrial DNA, or for epigenome editing, where changes in gene activity can be made without altering DNA sequences.

1.8. In 2016, for the first time, the HFEA granted a research license for a project using CRISPR Cas9 technology to study genetically modified embryos at the Francis Crick Institute. The work published from this project has included research into the impact of CRISPR-Cas9 on human

embryos including loss-of-heterozygosity (Lobato et al., 2021) and the role of specific genes in human embryogenesis (Fogarty et al., 2017).

1.9. Although work to improve the accuracy of CRISPR-Cas9 is ongoing, there are still improvements to be made to ensure that incorrect on-target as well as off-target errors do not occur. Errors should be rare with appropriate design of the guide RNAs. Furthermore, mosaicism may also be a problem for genome editing in embryos, where not all the cells may carry the desired edit. This could result in inaccurate genotyping (by PGT-M).

1.10. The possible clinical uses of heritable genome editing raise significant ethical, legal, and social concerns. This is in part due to the heritability of the changes, and that at present the methods are not yet considered safe or efficient enough for clinical applications in humans. At present, 'treatment' applications are considered to be those which would be most acceptable applications in the future. However, questions remain as to how to appropriately demarcate what 'treatment' means, which 'treatment' applications would be appropriate, and for whom this new technology should be made available.

1.11. There have been a significant number of research studies considering germline genome editing in animal embryos. This paper focuses on regulatory publications and ethical and legal discussions surrounding possible human clinical applications.

1.12. Genome editing was last discussed at SCAAC in October 2020. Horizon scanning outputs examined at SCAAC in 2021 and 2022 considered advances and publications in genome editing.

1.13. The aim of the committee's discussion of this topic is to highlight any other recent developments in terms of regulatory recommendations and to discuss the potential for clinical application of this technology. The committee are also asked to discuss social, ethical and legal considerations arising out of such developments for the Authority.

1.14. The Executive notes that the current paper provides a summary of publications identified in the specified time frame of when literature search was performed. This paper provides a summary of these publications, and is not an assessment of the views or position.

2. Recent developments in regulatory guidelines

2.1. There have been several publications in recent years which consider the legal, scientific, and ethical issues raised by the clinical application of germline genome editing.

2.2. The Third International Summit on Human Genome Editing took place in March 2023. The concluding Statement from the Organising Committee of the Third International Summit stated the following:

"Heritable human genome editing

Preclinical evidence for the safety and efficacy of heritable human genome editing has not been established, nor has societal discussion and policy debate been concluded. (In some cases, preimplantation genetic testing is among the alternatives.) Heritable human genome editing should not be used unless, at a minimum, it meets reasonable standards for safety and efficacy, is legally sanctioned, and has been developed and tested under a system of rigorous oversight that is subject to responsible governance. At this time, these conditions have not been met".

2.3. The International Society for Stem Cell Research (ISSCR) published updated guidelines in 2021 setting out fundamental ethical principles and guidelines for laboratory-based human embryonic stem cell research, embryo research, and related research activities.

2.4. The ISSCR guidelines places clinical research involving heritable genome editing into 'Category 3A' research. This research category is research activities that are 'currently not permitted. It is considered that "*Research under this category should not be pursued at this time because the approaches are currently unsafe or raise unresolved ethical issues. There may be valid reasons for undertaking the research in the future, but this should not proceed until the safety and ethical issues are resolved*". This, however, only applies to research where the modified embryos are then transferred to human uterus. That is, this prohibits clinical applications rather that laboratory research on germline cells and embryos.

2.5. Addressing heritable genome editing, the ISSCR guidelines state the following:

"Substantial preclinical research is needed to minimize the potential harm associated with clinical applications involving heritable genome editing; therefore, any attempt to modify the nuclear genome of human embryos for the purpose of reproduction is premature and should not be permitted at this time"

2.6. The ISSCR emphasises the need to have extensive preclinical research to minimise any harms arising from unintended on- or off-target modifications. Additionally, the guidelines state that eventual clinical applications should be restricted for interventions where there is "the most favourable balance of potential harms and benefits and this will be most clearly defined for diseases and patients for which there are no viable alternatives. This may include prospective parents for whom there are no or very limited available alternatives for preventing transmission of diseases and conditions for which mortality is high and morbidity is severe". The guidelines note that "Other options for having a healthy child, including adoption, gamete or embryo donation, and preimplantation genetic testing, should be considered with appropriate counselling prior to any decision to proceed."

2.7. The ISSCR guidelines also recommend that when the technical and safety issues are resolved, any uses of germline genome editing in humans should be "evaluated on a case-by-case basis" that should consider social and ethical issues of its application, not just scientific safety. Considerations include public opinion through "meaningful public engagement", a need for "robust regulations and oversight", and a restriction to prospective parents who "lack reasonable alternatives". Additionally, the recommendation notes in order to ensure that edits to not have "unintended deleterious consequences", any changes to the genome should be to change "a known pathogenic genetic variant to one that is present in unaffected family members, common in the relevant population, or known not to be disease-causing".

2.8. Finally, the ISSCR emphasised the importance of the scientific community to ensure that "premature or unethical" uses of genome editing do not take place until the "safety, ethical, and societal issues" are resolved. The ISSCR encourages researchers to "report unethical uses" to relevant bodies, funders, and regulators.

2.9. A recent briefing from the European Parliament published in 2022 highlights relevant principles of governance including ethical and legal pluralism, the importance of inclusive debate, and the need for transnational cooperation. The briefing goes on to highlight regulation and action

mechanisms at a European Union level and national level, as well as the international role that the EU should take in promoting regulatory efforts.

2.10. In 2022, the results of the UK Citizens' jury on genome editing were published. Conclusions of the jurors included that the majority agree that "the government should consider changing the law to allow intentional genome editing of human embryos for serious genetic conditions".

2.11. The Council of Europe published conclusions and clarifications of Article 13 of the Oviedo Convention which states that:

"Article 13 – Interventions on the human genome

An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants"

In this they clarified that any gametes, embryos, or precursors which have had their genome modified cannot be used within assisted reproduction. Additionally, they clarified that uses of germline genome editing for a 'preventative purpose' referred to the "occurrence of a disease or disorder".

2.12. Since the last SCAAC discussion, the World Health Organisation has published several key documents on human germline genome editing. These include a position paper summarising guidance from their published governance framework for human germline genome editing and recommendations on human germline genome editing. The recommendations span 9 key areas including international collaboration, the use of human genome editing registries, and the need to create clear ethical values and principles.

2.13. A significant publication from the National Academy of Medicine, National Academy of Sciences, and the Royal Society, 'Heritable Human Genome Editing' was published in late 2020. This 2020 publication, which was designed to consider a translational pathway, set out the then current state of scientific advances in genome editing prior to considering potential applications of heritable human genome editing. The report then suggested some aspects of a responsible governance system for clinical applications of human germline genome editing and examined current regulatory systems that were in place internationally.

2.14. The conclusions made by this report was noted as taking "quite bold steps" by Cohen and Adashi, 2021. Examples of the 'bold steps' included proposing a case-by-case approach to permitted used of germline genome editing in humans, and placing significant importance upon the "interest in having children who are genetically related" to prospective parents as a justification for its use.

2.15. Papers have noted the 'ambiguities' in regulation, and the need to work on international consensus to ensure responsible research, Ghosh et al., 2023. A paper by Chen et al., 2021 considers the conditions of Dr He's clinical application of germline genome editing in the twins Lulu and Nana. The paper examines the regulatory policies in place in China, and the role of the international research community. A paper in 2020 by Baylis et al., 'Human Germline and Heritable Genome Editing: The Global Policy Landscape' set out the policies on human germline genome editing for reproduction and for purposes other than reproduction (e.g. research) across over 100 countries. The summary showed that most (but not all) countries surveyed had prohibition of the use of germline genome editing within reproduction, but that there were more

countries that permitted (or had exceptions to the prohibition) for research uses of human genome editing.

3. Social and ethical research

3.1. A paper by Turocy et al., 2021, reviews the possible adverse effects of applying genome editing including large deletions, chromosomal changes, and mosaicism. The review goes on to examine base and prime editing in human embryos and summarises advances made in the editing of in vitro-derived gametes and embryos. Finally, key ethical issues raised by clinical human applications of germline genome editing are considered including those related to beneficence, balancing possible risks and benefits, and equitable access.

3.2. A review by Greenfield, 2021, considers scientific and ethical considerations related to the use of heritable genome editing in humans, examining applications within assisted reproduction. Further papers considering the need for further research into the ethical issues include Nadimpally, 2023, Labude et al., 2022, and Lau 2023.

3.3. A paper by MacKellar, 2021, examines equality issues related to the application of heritable genome editing in humans. In de Miguel Beriain, 2021, further ethical issues are touched upon including issues of risk and reproductive choice. The paper also considers the differences between heritable genome editing and pre-implantation genetic diagnosis.

3.4. The ethical differences between heritable genome editing in embryos and foetal gene therapy is discussed in Mattar et al., 2021. The paper considers the different levels of clinical data available and the different ethical issues that the application of the technologies raises. A further paper by Xafis et al., 2021, uses political, ethical, and social lenses to consider issues within clinical applications of heritable genome editing in humans.

3.5. Further work into the ethical perspectives of human applications of heritable genome editing include a review by Joseph et al., 2022, which looks at public perspectives regarding heritable genome editing, philosophy and ethics publications, and human research ethics.

3.6. Farrell et al., 2022, consider the ethical implications beyond future humans who have had their germline genome edited, considering the implications for the women who will be pregnant with embryos that have had genome editing applied, as well as the families of the resultant children.

3.7. A paper by Shozi and Thaldar 2023, discusses the importance of equal access to clinical uses of germline genome editing and the importance of reflecting upon future generations when considering the development of the technology for clinical use.

3.8. A paper by Shozi, 2021, investigates whether human heritable genome editing violates human dignity through an African perspective.

3.9. Empirical work by Sawai et al., 2023, investigated the views of Japanese expert and lay audiences towards clinical applications of germline genome editing in humans. The survey examined which possible applications of heritable germline genome editing in humans would be considered the most 'acceptable' and noted the importance of holding public discussion with varied stakeholders.

3.10. A paper by Peng et al., 2022, considers the advances in the ethics governance of human germline genome editing and China and considers how the regulatory system can be further developed.

3.11. Articles including Nelson et al., 2021, have critically reviewed discourses about clinical applications of germline genome editing in humans, highlighting the importance of public engagement. Furthermore, Yu et al., 2021, discuss the importance of inclusive global governance of germline genome editing. In this paper they note the need to ensure global collaboration, and not focus only on the views of only some countries, and the need for "open and inclusive platforms for dialogue". The value of public deliberation in the governance of human genome editing is also discussed in Kamenova 2023. A paper by Conley et al., 2023, however, questions the value of public engagement and discusses whether public engagement produces more "equitable processes or policy outcomes". Finally, a paper by Benston, 2022, propose how to include public engagement and stakeholder surveys to ensure that policies surrounding clinical applications of human germline genome editing are ethical.

3.12. A paper by Thaldar et al., 2022, discusses a public engagement exercise that took place in South Africa to examine views on clinical uses of germline genome editing in humans. The exercise identified the difference in public views towards applications for different purposes, and the discussion surrounding risks and benefits of applications of this novel technology. Further issues discussed included the importance of access to clinical uses of germline genome editing.

3.13. Additional work on how clinical applications of heritable human genome editing should be regulated includes Nicol et al., 2022, which considers its regulation in Australia, and a piece by Saldaña-Tejeda et al., 2022 which provides a perspective from Latin America.

3.14. Safety is a key scientific and ethical concern when considering when it will be appropriate to move from in vitro research to in vivo research of germline genome editing in humans. A paper by Baxter, 2021, criticises the current policy proposals that have attempted to address safety considerations, arguing that they have been insufficient or unhelpful in their framing.

3.15. Two recent bioethics papers, one by Douglas and Devolder, 2022 and another by Sparrow, 2022, examine the application of germline genome editing will benefit or harm the same identity and thereby future persons.

4. Conclusions

4.1. The HFE Act does not permit interventions in the nuclear DNA of gametes or zygotes for the purposes of germline genome editing in reproduction. The last SCAAC review of studies using genome editing techniques on human and animal embryos was presented to the committee in 2020.

4.2. Reports discussing the regulatory framework on genome editing consider that:

- Preclinical evidence for the safety and efficacy of heritable human genome editing has not been established and there remains significant concern about the safety and efficacy of the technology.
- Substantial preclinical research is needed to minimise the potential harm associated with clinical applications involving heritable genome editing

- Heritable human genome editing should not be used unless, at a minimum, it meets reasonable standards for safety and efficacy, is legally sanctioned, and has been developed and tested under a system of rigorous oversight that is subject to responsible governance.
- Eventual clinical applications should be restricted for interventions for diseases and patients for which there are no viable alternatives. Such intervention should only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants.
- Heritable applications of human genome editing may be acceptable in the future under certain circumstances.
- Further societal discussion and policy debate need to be undertaken

4.3. Significant further scientific research into improving the accuracy of genome editing technologies is required before germline applications can take place. Furthermore, work and discussion around the ethical and social issues needs to continue to respond to questions and concerns raised about clinical applications in humans. This may include establishing which applications might be considered to be acceptable in the future, and for whom should applications be made available for.

5. Recommendations

5.1. The committee is asked to note this update and:

- advise the executive if they are aware of any other recent developments;
- discuss the potential for clinical application of this technology and identify particular concerns or issues that should be highlighted; and
- review whether any outputs from the HFEA are required.

6. References

Alanis-Lobato G, Zohren J, McCarthy A, Fogarty NME, Kubikova N, Hardman E, Greco M, Wells D, Turner JMA, Niakan KK. Frequent loss of heterozygosity in CRISPR-Cas9-edited early human embryos. *Proc Natl Acad Sci U S A* 2021;118:e2004832117.

Baxter J. When is it Safe to Edit the Human Germline? *Sci Eng Ethics* 2021;27:43.

Baylis F, Darnovsky M, Hasson K, Krahn TM. Human Germline and Heritable Genome Editing: The Global Policy Landscape. *The CRISPR Journal* 2020;3:365–377. Mary Ann Liebert, Inc., publishers.

Benston S. Walking a Fine Germline: Synthesizing Public Opinion and Legal Precedent to Develop Policy Recommendations for Heritable Gene-Editing. *J Bioeth Inq* 2022;19:421–431.

Chen Q, Ma Y, Labude M, Schaefer GO, Xafis V, Mills P. Making sense of it all: Ethical reflections on the conditions surrounding the first genome-edited babies. *Wellcome Open Res* 2021;5:216.

Cohen IG, Adashi EY. Legal and Ethical Issues in the Report Heritable Human Genome Editing. *Hastings Center Report* 2021;51:8–12.

Conley JM, Cadigan RJ, Davis AM, Juengst ET, Kuczynski K, Major R, Stancil H, Villa-Palomino J, Waltz M, Henderson GE. The Promise and Reality of Public Engagement in the Governance of Human Genome Editing Research. *Am J Bioeth* 2023;23:9–16.

Council of Europe. Intervention on the human genome: re-examination process of Article 13 of the *Oviedo Convention*. 2022a;.

Council of Europe. Genome editing technologies: final conclusions of the re-examination of Article 13 of the Oviedo Convention - Human Rights and Biomedicine. 2022b; Available from: https://www.coe.int/en/web/bioethics/-/genome-editing-technologies-final-conclusions-of-the-re-examination-of-article-13-of-the-oviedo-convention.

Douglas T, Devolder K. Gene Editing, Identity and Benefit. The Philosophical Quarterly 2022;72:305–325.

European Parliament. *Genome editing in humans: A survey of law, regulation and governance principles*. 2022;

Farrell RM, Malek J, Thomas Scott C. Beyond babies: Implications of human genome editing for women, children, and families. *Account Res* 2022;29:67–76.

Fogarty NME, McCarthy A, Snijders KE, Powell BE, Kubikova N, Blakeley P, Lea R, Elder K, Wamaitha SE, Kim D, et al. Genome editing reveals a role for OCT4 in human embryogenesis. *Nature* 2017;550:67–73.

Ghosh S, Ghosh S, Raghunath M, Bhaskar R, Sinha JK. Balancing potential benefits and ethical considerations of gene editing. *Lancet* 2023;401:2109–2110.

Greenfield A. Making sense of heritable human genome editing: Scientific and ethical considerations. *Prog Mol Biol Transl Sci* 2021;182:1–28.

International Society for Stem Cell Research. *ISSCR Guidelines for stem cell research and clinical translation.* 2021;

Joseph AM, Karas M, Ramadan Y, Joubran E, Jacobs RJ. Ethical Perspectives of Therapeutic Human Genome Editing From Multiple and Diverse Viewpoints: A Scoping Review. *Cureus* 2022;14:e31927.

Kamenova K. The Intrinsic Value of Public Deliberation in the Governance of Human Genome Editing. *The American journal of bioethics : AJOB* [Internet] 2023;23:. Am J Bioeth.

Labude MK, Xafis V, Lai PS, Mills C. Vulnerability and the Ethics of Human Germline Genome Editing. *The CRISPR Journal* 2022;5:358–363.

Lau PL. Evolved Eugenics and Reinforcement of “Othering”: Renewed Ethico-Legal Perspectives of Genome Editing in Reproduction. *BioTech* 2023;12:51.

MacKellar C. Why human germline genome editing is incompatible with equality in an inclusive society. *New Bioeth* 2021;27:19–29.

Mattar CNZ, Labude MK, Lee TN, Lai PS. Ethical considerations of preconception and prenatal gene modification in the embryo and fetus. *Hum Reprod* 2021;36:3018–3027.

Miguel Beriain Í de. The Geneva Statement on Heritable Human Genome Editing: A Criticism. *Trends in Biotechnology* 2021;39:219–220.

Nadimpally S. The ethics, equity, and governance of human genome editing need greater consideration. *BMJ* 2023;381:996.

National Academy of Medicine, National Academy of Sciences, and the Royal Society. *Human Genome Editing: Science, Ethics, and Governance.* 2017;

Nelson JP, Selin CL, Scott CT. Toward Anticipatory Governance of Human Genome Editing: A Critical Review of Scholarly Governance Discourse. *J Responsible Innov* 2021;**8**:382–420.

Nicol D, Rudge C, Paxton R, Niemeyer S. How Should We Regulate Heritable Human Genome Editing in Australia? *J Law Med* 2022;**29**:322–336.

Peng Y, Lv J, Ding L, Gong X, Zhou Q. Responsible governance of human germline genome editing in China†. *Biol Reprod* 2022;**107**:261–268.

Saldaña-Tejeda A, Aparicio A, González-Santos SP, Arguedas-Ramírez G, Cavalcanti JM, Shaw MK, Perler L. Policy landscapes on human genome editing: a perspective from Latin America. *Trends Biotechnol* 2022;**40**:1275–1278.

Sawai T, Hatta T, Akatsuka K, Fujita M. Human genome editing in clinical applications: Japanese lay and expert attitudes. *Frontiers in Genetics* [Internet] 2023;**14**.

Shozi B. Does human germline genome editing violate human dignity? An African perspective. *J Law Biosci* 2021;**8**:lsab002.

Shozi B, Thaldar D. Promoting Equality in the Governance of Heritable Human Genome Editing Through Ubuntu: Reflecting on a South African Public Engagement Study. *American Journal of Bioethics* 2023;**23**:43–49.

Sparrow R. Human Germline Genome Editing: On the Nature of Our Reasons to Genome Edit. *The American Journal of Bioethics* 2022;**22**:4–15.

Statement from the Organising Committee of the Third International Summit on Human Genome Editing 2023;

Thaldar D, Shozi B, Steytler M, Hendry G, Botes M, Mnyandu N, Naidoo M, Pillay S, Slabbert M, Townsend B. A deliberative public engagement study on heritable human genome editing among South Africans: Study results. *PLoS One* 2022;**17**:e0275372.

Turocy J, Adashi EY, Egli D. Heritable human genome editing: Research progress, ethical considerations, and hurdles to clinical practice. *Cell* 2021;**184**:1561–1574.

Wellcome Connecting Science. Report of the UK Citizens Jury on Human Embryo Editing. 2022; Available from: https://societyandethicsresearch.wellcomeconnectingscience.org/project/uk-citizens-jury-on-genome-editing/.

World Health Organization. Human genome editing: recommendations. 2021a; Available from: https://www.who.int/publications/i/item/9789240030381.

World Health Organization. Human genome editing: a framework for governance. 2021b; Available from: https://www.who.int/publications/i/item/9789240030060.

World Health Organization. Human genome editing: position paper. 2021c; Available from: https://www.who.int/publications-detail-redirect/9789240030404.

Xafis V, Schaefer GO, Labude MK, Zhu Y, Holm S, Foo RS-Y, Lai PS, Chadwick R. Germline genome modification through novel political, ethical, and social lenses. *PLoS Genet* 2021;**17**:e1009741.

Yu H, Xue L, Barrangou R, Chen S, Huang Y. Opinion: Toward inclusive global governance of human genome editing. *Proc Natl Acad Sci U S A* 2021;**118**:e2118540118.

Artificial intelligence, robotics and automation in fertility treatment

Details about this paper

Area(s) of strategy this paper relates to:	Shaping the future
Meeting:	Scientific and Clinical Advances Advisory Committee (SCAAC)
Agenda item:	9
Paper number:	HFEA (05/02/2024) 009
Meeting date:	05 February 2024
Author:	Emily Staricoff, Policy Manager (Science and Engineering Fast Stream)
Annex:	Annex A: Application of the HFEA Code of Practice to AI, robotics and automation

Output from this paper

For information or recommendation?	For recommendation
Recommendations:	• Advise of any other relevant recent developments in AI, robotics and automation in fertility treatment. • Discuss which aspects of AI, robotics and automation in fertility treatment the Executive should focus on, as part of the Authority's work on this topic going forward. • Review whether any outputs from the HFEA are required, to address the use, or regulation, of AI, robotics and automation in fertility treatment.
Resource implications:	In budget
Implementation date:	Recommendations will be implemented as soon as feasible
Communication(s):	To be determined
Organisational risk:	Low

1. Introduction

1.1. Artificial intelligence (AI) is the theory and development of computer systems that can mimic cognitive functions or perform tasks normally associated with human intelligence. The government defines AI by two characteristics that generate the need for a bespoke regulatory response: adaptivity and autonomy (2023a). Machine learning (ML) is a subset of AI techniques that give computers the ability to learn and perform tasks without explicit instructions. For simplicity, further subsets of AI or ML are not referenced in this paper.

1.2. The HFEA regulates fertility treatment that takes place within UK licensed fertility clinics. Our regulatory remit includes all methods by which authorised processes are carried out, including if AI, robotics and automation are used. Annex A provides examples of how the HFEA Code of Practice applies to the uses of AI in fertility clinics within our existing regulatory framework:

1.3. AI was last discussed by the Scientific and Clinical Advances Advisory Committee (SCAAC) in October 2022. The **discussion** included how the HFEA's regulatory remit regarding AI could be translated into laboratory and clinical practices; highlighting the distinction between when AI is a 'new way of doing an old thing' or a 'new way of doing a new thing'; and when an authorised process would be deemed sufficiently different if AI is used.

1.4. This paper provides an overview of the findings from recent publications relevant to the use of AI, robotics and automation in fertility treatment. The Executive notes that the current paper provides a summary of results as described in publications, but does not provide an assessment or comment on the validity of studies.

1.5. A reference list of relevant papers on this topic published up until 19 December 2022 was included in the horizon scanning paper presented to the SCAAC in February 2023. Therefore, this paper only includes a summary of the results of publications between 19 December 2022 – 31 December 2023.

1.6. The review of literature related to time-lapse imaging will be undertaken separately as part of the treatment add-ons review process, and therefore is not included here. Other topics that were prominent in the search results, but not included here due to being outside of the HFEA's regulatory remit, were research into the use of AI: during pregnancy and associated complications, including gestational diabetes; in endometriosis; in miscarriage; to improve general health and wellbeing that in turn impacts upon fertility; and in livestock reproduction (namely cattle, sheep and poultry).

1.7. The aim of the committee's discussion of this topic is to get an idea of the current and future uses of AI within fertility treatment and if the committee think there may be significant implications for licensing and regulation arising out of such developments or social, ethical and legal considerations for the Authority.

2. Reviews and opinion pieces

2.1. A Nature News Feature highlighted the current and potential limitations of emerging generalist AI models in medicine (Lenharo, 2023). Similarly, the strengths and limitations of using AI in assisted reproductive technology (ART) has been summarised (Jiang *et al.*, 2023c). A distinction between 'narrow' and 'general' applications of AI was highlighted, with a focus on the application of 'narrow' AI in fertility (Miloski, 2023).

2.2. Reviews of the emerging uses, applications, and advancements of AI in andrology, reproductive medicine and the fertility sector have proposed how the reliable, objective, and timely nature of AI could be used to improve several treatment and laboratory processes and procedures (Ghayda *et al.*, 2023; Glatstein *et al.*, 2023; Jiang and Bormann, 2023a).

2.3. Reviews have also focused on a specific element of the use of AI in fertility and embryology, including in ovarian stimulation (Hariton *et al.*, 2023); cryostorage (Go and Hudson, 2023); and sperm, oocyte and embryo assessment and selection (Cherouveim *et al.*, 2023b; Gill and Quaas, 2023; Lustgarten Guahmich *et al.*, 2023; Si *et al.*, 2023). The potential uses of the Internet of Things in embryology laboratories (Palmer *et al.*, 2023), and the potential for multiomic and wearable technologies to improve diagnosis, prognosis and management of female reproductive health have also been reviewed (Kharb and Joshi, 2023). Collectively, these reviews highlight the valuable assistance to embryologists that AI tools can provide, mainly due to their data processing capability and objectivity. It is also noted that the potential clinical benefits to a single treatment cycle remain yet to be established, and that clinical embryologists should maintain expertise to ensure safety and oversight of these technologies.

2.4. A series of operational, cultural and maintenance considerations for the evaluation of AI tools in practical and clinical contexts has been discussed (Letterie, 2023), and criteria for the accurate and safe implementation of AI in ART laboratories has been proposed (Güell, 2023). A standardised framework for system-level and holistic evaluation of interacting AI and digital health tools has also been proposed (Welzel *et al.*, 2023).

3. Developments in basic science

3.1. ML tools have been developed to assist researchers with embryo segmentation, such as the approach presented by (Tran *et al.*, 2023). Additionally, an automatic single pipeline for the segmentation of all morphological structures during blastocyst development stages has been developed (Farias *et al.*, 2023). An open-source ML tool, called the Mouse Embryo Multi-Organ Segmentation (MEMOS), which provides a rich analysis resource has been published (Rolfe *et al.*, 2023). Finally, a ML pipeline to perform embryonic heart structure segmentation has been developed (Ling *et al.*, 2023).

3.2. Other ML models that have been developed for use in embryo research include:

- EmbryoNet, presented in Nature Methods, for automated phenotyping through the linkage of phenotypic features to signalling pathways (Čapek *et al.*, 2023).
- insideOutside for the classification of interior and exterior cells of an early mouse embryo (Strawbridge *et al.*, 2023).
- A model to identify and track nuclei in developing embryos, and reconstruct whole-embryo cell lineages, presented in Nature Biotechnology (Malin-Mayor *et al.*, 2023).
- An automated workflow for extracting the contours of zebrafish embryos (Kondow *et al.*, 2023).

3.3. A ML method to determine the projection orientation of ellipsoidal-like cells, which could be used to investigate sperm cell activity has been developed (Zhao *et al.*, 2023). Additionally, an AI model to classify immature germinal vesicle oocytes, as surrounded nucleolus or not surrounded nucleolus has been trained (Veiga *et al.*, 2023).

3.4. Semrl et al. (Semrl *et al.*, 2023) assessed the feasibility of using Chat Generative Pre-trained Transformer (ChatGPT) to assist academic writing in the field of human reproduction. Whilst

ChatGPT could efficiently summarise information, it could not be relied upon to perform literature searches, interpret data or provide accurate source citation. The authors encouraged transparency around the use of AI in academic writing.

4. Clinic facing advancements

4.1. Predictive AI models have been developed to assist healthcare professionals in decision making:

- One group developed and published four different models to predict live birth rates following fresh or frozen in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI), and one was found to have good predictive performance (Liu *et al.*, 2023b). A different group also developed a predictive model and achieved a peak accuracy of approximately 65%, but it was noted that this would need to be improved before implementation (Louis *et al.*, 2023).
- Models that incorporate an individual's medical history or clinical characteristics to predict the most optimal fertility treatment strategy or live birth outcomes have also been developed (Li *et al.*, 2023a; Liu *et al.*, 2023a; Majumdar *et al.*, 2023; Wang *et al.*, 2023a).

4.2. AI-based methods for assessing sperm DNA fragmentation have been developed, including prediction tools (Kumar *et al.*, 2023; Noy *et al.*, 2023), and novel sperm chromatin dispersion assays (Hsu *et al.*, 2023; Kuroda *et al.*, 2023). Relatedly, ML has been used to explore the combined effect of performing sperm DNA fragmentation assays following routine semen analysis (Peng *et al.*, 2023).

4.3. Several AI models to predict ploidy status of blastocysts or embryos have been developed and were summarised in a recent review (Jiang and Bormann, 2023b). The performance of a commercially available embryo assessment algorithm was compared to conventional morphological evaluation (Valera *et al.*, 2023), and the performance of 12 ML models for blastocyst ploidy prediction were compared (Bamford *et al.*, 2023). Similarly, it has been reported that AI-based pre-implantation genetic testing for aneuploidy (PGT-A) may increase ongoing pregnancy and live birth rates when compared to next-generation sequencing based PGT-A (Buldo-Licciardi *et al.*, 2023). It has been found that including patient characteristics improves the accuracy of embryo ploidy prediction models (Jiang *et al.*, 2023a), and an AI model that combined morphokinetic and morphological characteristics of blastocysts with clinical parameters was developed (Yuan *et al.*, 2023). Another ML model, called the Attentive Multi-Focus Video and Clinical Information Fusion Network (AMCFNet), has also been developed (Chen *et al.*, 2023a). Finally, 'STORK-A', was published in the Lancet Digital Health, and is a non-invasive automated AI method of embryo selection using prediction of embryo ploidy status (Barnes *et al.*, 2023). An associated editorial highlighted the recommendation for this to be used as a decision-making tool, rather than to replace traditional methods (The Lancet Digital Health, 2023).

4.4. AI models have been developed to assist healthcare professionals with embryo assessment and selection. For example, a fully automated ML model for the evaluation of human embryos, iDAscore v2.0, has been developed and validated (Theilgaard Lassen *et al.*, 2023). When iDAScore v1.0 was compared with iDAScore 2.0, which has 15% more training data than v1.0, it was found that the model's performance was improved by increasing the size of the training data (Ueno *et al.*, 2023). Several other publications have utilised iDAscore v2.0, including comparisons of the model output with conventional manual assessments (Ahlström *et al.*,

2023; Zhu *et al.*, 2023a). Of note, TFP Fertility partnered with Vitrolife (the developers of iDAScore) to conduct the *eValuating iDA Selection Ability (the VISA Study)* at four of their clinics across the UK. This study is currently active (as of 31 December 2023) and aims to compare the embryo selection performance of iDAScore with trained embryologists. Quantitative ML models for blastocyst have also been developed (Charnpinyo *et al.*, 2023; Zheng *et al.*, 2023).

4.5. Studies have compared AI-based embryo ranking and selection to embryologists. One study found a high degree of agreement between the embryologists, but a lower level between the AI models, and between the embryologists and the AI algorithms (Zaninovic *et al.*, 2023). Another study found that AI outperformed clinical teams (Salih *et al.*, 2023). Since its publication, this study has been discussed in a Letter to the Editor (Hengstschläger, 2023), and a subsequent reply (Horta *et al.*, 2023). A dataset of static morphological images intended for use in training ML models that support clinical embryologists with the embryo selection procedure has also been published (Kromp *et al.*, 2023).

4.6. It has been found that ML models could accurately identify key morphologic landmarks that are used to guide embryologists during micromanipulation procedures (Jiang *et al.*, 2023b), and that ML models can be trained to characterise the temporal heterogeneity of embryo preimplantation development (Zabari *et al.*, 2023).

4.7. ML tools have been developed to identify embryos with a high risk of miscarriage (Amitai *et al.*, 2023), and to investigate the most important predictor of Day 5 blastocyst utilisation rate (Serdarogullari *et al.*, 2023).

4.8. Studies have highlighted the importance of explainability or interpretability of AI models, termed 'glass-box AI'. For example, the importance of model explainability was highlighted by a meta-analysis that explored the use of AI for predicting infertility or treatment related risks (GhoshRoy *et al.*, 2023a), and it has been shown that an interpretable AI system can assist embryologists to improve the implantation rate of single blastocyst transfer (Wang *et al.*, 2023b). A novel classification system for traditional and AI systems in embryology has been proposed that focuses on subjectivity, explainability and interpretability (Lee *et al.*, 2023b).

5. AI models to predict or improve treatment outcomes

5.1. A ML model to predict the time of ovulation and optimal fertilisation window for performing intrauterine insemination (IUI) or timed intercourse has been developed (Youngster *et al.*, 2023). Additionally, an AI model to predict lack of pregnancy following IUI has been developed, and it was noted that provision of a pregnancy prognosis could enable straight referral to the most appropriate treatment pathway, reducing the time and cost to pregnancy (Garcia-Grau *et al.*, 2023).

5.2. A ML model to predict oocyte maturation rate in gonadotropin-releasing hormone (GnRH) antagonist cycles has been developed (Houri *et al.*, 2023).

5.3. ML models to predict the outcome of frozen embryo transfer (FET) have also been developed, including a model to identify predictive factors of live birth outcomes following first FET (Jin *et al.*, 2023); a model to predict the risk factors that cause first trimester pregnancy loss in FET cycles (Ozer *et al.*, 2023); a model that combines ultrasound with clinical quantitative variables to non-invasively predict the outcome of FET (Liang *et al.*, 2023); and a model to analyse endometrial histology to predict the chance of pregnancy following FET (Li *et al.*, 2023b).

5.4. Finally, an AI algorithm was used to identify an association between a large blastocyst size and higher implantation potential (Fruchter-Goldmeier *et al.*, 2023), and it was demonstrated that combining ML models with metabolomic and embryologic data improved the prediction of embryo implantation potential (Cheredath *et al.*, 2023).

6. Uses of AI in male fertility, semen and sperm assessment

6.1. Seven ML models for the assessment of male fertility were compared, and it was noted that increasing the explainability and transparency of AI models helps clinicians to understand the prediction process and verify the results given (GhoshRoy *et al.*, 2023b). Additionally, a range of ML models to predict the success of testicular sperm extraction in patients with nonobstructive azoospermia have been compared (Bachelot *et al.*, 2023).

6.2. ML algorithms have been developed to identify risk factors affecting sperm count (Huang *et al.*, 2023a), and this work was subsequently built on to develop a predictive model for sperm count assessment (Huang *et al.*, 2023b).

6.3. An opinion piece was published (Sengupta *et al.*, 2023) to highlight the findings from a poster that was presented at the 2022 European Society for Human Reproduction and Embryology (ESHRE) conference that introduced a new AI semen analysis system, called Mojo AISA, which offers superior performance compared to conventional semen analysis systems (Parrella *et al.*, 2022). Additionally, a ML approach, called SwinMobile, was developed to classify sperm morphology (Mahali *et al.*, 2023).

7. Advancements in robotics

7.1. The first report of babies to be conceived using automated ICSI has been published (Costa-Borges *et al.*, 2023). In a small clinical pilot trial, the robot was operated by engineers with no experience of micromanipulation and demonstrated similar results to those obtained with manual ICSI conducted by experienced embryologists.

7.2. It has also been found that single-incision robotic myomectomy was an effective, feasible, safe and timely method to remove symptomatic fibroids (Kim *et al.*, 2023), and that single-site robotic ovarian cystectomy could be a promising new therapeutic option for complex cases to avoid an additional side port (Lee *et al.*, 2023a). The use of robotic-integrated ultrasound has also been demonstrated (Hardman *et al.*, 2024).

7.3. An automated method to prepare IVF or embryo culture dishes, alleviating the need for manual preparation, has been developed and validated (in mice) (Zhu *et al.*, 2023b), as well as an automated vitrification and thawing system (Zhu *et al.*, 2023c).

8. Digital health interventions

8.1. Studies have focused on the use of digital health interventions during fertility patient' journeys. It was found that use of an online app (myFertiCare) improved patient's treatment knowledge and enhanced the experience of patient-centred care (Sparidaens *et al.*, 2023). Additionally, it has been shown that personalisation and localisation were the two core concepts required for successful development, implementation and adoption of digital health interventions before, during and after pregnancy (Lee *et al.*, 2023c). It has also been shown that an AI platform can

be used to increase completion rates of diagnostic tests prior to initiating fertility treatment (Acker *et al.*, 2023).

8.2. Whilst is has been found that menstrual tracking apps can provide quick, scalable and cost-effective methods for collecting data in reproductive health research (Shea *et al.*, 2023), in September 2023, the Information Commissioner's Office (ICO) announced a review of period and fertility tracking apps due to concerns over data security (Information Commissioner's Office, 2023).

8.3. It has also been highlighted that use of consistent and reliable adherence reporting metrics are an important area for improving clinical trials of digital health apps (Grayek *et al.*, 2023).

9. Ethical considerations on the use of AI in the fertility sector

9.1. Examinations of the ethical challenges surrounding the introduction of AI into reproductive medicine have highlighted the following ethical principles: responsibility and accountability; transparency and interpretability; fairness and representability; efficacy and trust; data protection and usage; informed consent and privacy (Coghlan *et al.*, 2023; Rolfes *et al.*, 2023).

9.2. How algorithmic biases result in healthcare disparities was highlighted in a Nature Biomedical Engineering Perspective (Chen *et al.*, 2023b). The importance of accounting for differences in patient characteristics and clinic-specific conditions during evaluation or comparison of AI model performance across different clinics has also been highlighted (Johansen *et al.*, 2023).

9.3. An exploration of the use of chatbots for reproductive health education and advice found that whilst chatbots were acceptable for appointment booking and general advice, chatbots were not acceptable for safeguarding, diagnosis or emotional support (Nadarzynski *et al.*, 2023).

10. Regulatory and legal considerations on the use of AI in the fertility sector

10.1. The increased use of AI as part of medical treatment has been accompanied by commentary about the regulatory and legal considerations related to such developments. This section summarises relevant regulatory and legal considerations that have been raised through pieces that were published during the timeframe used for this paper's literature search.

10.2. The importance of rights-based approaches being taken during all phases of development, implementation and evaluation of digital health tools for reproductive healthcare has been highlighted (Luigi-Bravo *et al.*, 2023), and that the approach to regulating AI in healthcare should be based on the human right to science, which obliges regulators to ensure that those interested can 'enjoy the benefits of scientific progress and its applications' (Ho, 2023).

10.3. A Nature comment piece called for the establishment of an official scientific body to audit AI systems and maintain a set of 'living guidelines' on the use, regulation and legislative developments related to AI (Bockting *et al.*, 2023). Following the world's first conference on AI in fertility (Curchoe, 2023a), the AI Fertility Society was launched, which will aim to provide professional leadership and frameworks around the provision, regulation and implementation of AI in fertility.

10.4. Governments and academic institutions have been called upon to facilitate data accessibility to drive innovation in software as a medical device (Yu *et al.*, 2023). Additionally, the scope of

regulation, including what exactly is, or should be, regulated as medical devices has been discussed (Wyatt *et al.*, 2023). It has been highlighted that regulating AI-based medical devices requires a "multifaceted approach that considers policy changes, data diversity, real-world evidence, cybersecurity, and postmarket surveillance", as well international harmonization of regulatory requirement (Curchoe, 2023b).

10.5. The regulatory history, and current regulatory landscape, of digital therapeutics has been reviewed, with a focus on how the Food and Drug Administration (FDA) is adapting frameworks to balance risk and speed, with reasonable and flexible regulation (Watson *et al.*, 2023). Additionally, the impact of existing regulatory frameworks on the intersection between connected health technological and medical products has been discussed, with a call for optimisation of the validation process; upskilling and expansion of the regulatory workforce; and increased knowledge-sharing among regulators (Awad *et al.*, 2023).

10.6. The World Health Organization (WHO) called for 'safe and ethical AI for health' (World Health Organisation (WHO), 2023). Whilst enthusiastic about the appropriate use of AI, WHO raised concerns about its rapid adoption including bias in data training sets, data protection, generation of misleading or inaccurate information, and adoption of untested systems.

10.7. The use of an AI quality assurance tool to monitor the expected versus observed performance of individual healthcare professionals performing ART procedures has been evaluated (Cherouveim *et al.*, 2023a). Additionally, it was found that an automated digital staff management platform to assess the inter- and intra- variability in embryologists' clinical decision-making was effective to increase regulatory compliance (Curchoe *et al.*, 2023a).

11. Relevant policy developments

11.1. There has been significant activity in the AI policy space worldwide, including across the UK government, government agencies and partner organisations. Such activity has included both cross-cutting and sector specific initiatives. This section summarises the most relevant policy-related developments and activities published upon within the timeframe used for this paper's literature search.

11.2. In January 2023, the Department of Health and Social Care announced 'shaping and supporting the health and social care workforce of the future' as an area of research interest, which included AI-assisted diagnoses and robotic surgery as priority topics.

11.3. In March 2023, the government published the 'pro-innovation approach to AI regulation' white paper (www.gov.uk, 2023a), which proposed a framework for AI regulation. In August 2023, the Science, Innovation and Technology Committee published an interim Report on their inquiry into the governance of artificial intelligence (www.publications.parliament.uk, 2023b), which highlighted the rapid rate of AI development and set out 12 challenges that the governance of AI must address, including bias, privacy, transparency, and liability. Whilst the Report welcomes the government's AI white paper, it noted that it already risks falling behind and relies heavily on existing regulatory systems, with the promise of central support. The report suggested a gap analysis is done of existing regulators to understand capacity and the possibility of the need for new regulatory powers. The government's response to the interim Report reiterated the ongoing work to establish a framework for AI regulation and a range of central support functions for regulators (www.publications.parliament.uk, 2023c).

11.4. The Government Chief Scientific Adviser conducted a review of how pro-innovation regulation can support regulated industries (www.gov.uk, 2023b) that included recommendations to encourage pro-innovation regulation, for which an implementation plan has been published (www.gov.uk, 2023c).

11.5. Chair's summaries of roundtable discussions held at the AI Safety Summit have been published (www.gov.uk, 2023d, 2023e). The Bletchley Declaration on AI (www.gov.uk, 2023f) established a shared understanding of opportunities and risks posed by frontier AI. The AI Safety Institute was launched (www.gov.uk, 2023g) to examine, evaluate, and test the safety of frontier AI.

11.6. The government launched the Fairness Innovation Challenge (www.gov.uk, 2023h), which will fund the development of innovative solutions to tackle bias and discrimination in AI systems, focusing on ensuing fairness of AI in healthcare. The AI Life Sciences Accelerator Mission was also announced, to drive the use of AI in life sciences and healthcare (www.gov.uk, 2023i).

11.7. The Medicines & Healthcare products Regulatory Agency's (MHRA's) 'Software and AI as a Medical Device Change Programme – Roadmap' (www.gov.uk, 2023j) aims to ensure that regulatory requirements for software and AI are clear, and that patients are protected. In October 2023, MHRA announced plans to progress a new 'regulatory sandbox', called the AI-Airlock (www.gov.uk, 2023k), which will facilitate faster access to emerging technologies ahead of gaining regulatory approval.

11.8. The AI and Digital Regulations Service for health and social care was launched (www.digitalregulations.innovation.nhs.uk, n.d.), which is a collaboration between MHRA, CQC, HRA, and NICE. The service also works closely with the NHS Innovation Service and is funded by the NHS AI Lab. The service aims to support the development and adoption of technologies in health and social care by mapping out the regulatory and health technology assessment pathway for AI and digital technologies.

11.9. The Government Centre for Data Ethics and Innovation and the Government Central Digital & Data Office have established the Algorithmic Transparency Recording Standard Hub (www.gov.uk, 2023l), which encourages public sector organisations to provide information about the algorithmic tools they use for decision-making, which is made publicly available.

11.10. The Chair of the Science, Innovation and Technology Committee noted that it was unlikely that significant AI legislation would be passed before 2025 (www.publications.parliament.uk, 2023a). Meanwhile, the Council of the EU have proposed the AI act, which is a flagship legislative initiative likely to set a global standard for AI regulation (Council of the EU, 2023).

12. Conclusion

12.1. The rapid development of AI, robotics and automation has the potential to bring great benefits to the fertility and embryology sector. The objective data processing capabilities of AI models can facilitate improved decision-making, increased efficiency, and greater standardisation both within, and between, fertility clinics. The implementation of these technologies into the sector requires the consideration of several factors, including ensuring safety, privacy, and traceability; establishing training, testing and validation requirements; ensuring transparency and communication of information between clinics and patients.

13. Recommendations

13.1. Members are asked to:

- Advise of any other relevant recent developments in AI, robotics and automation in fertility treatment.
- Discuss which aspects of AI, robotics and automation in fertility treatment the Authority should focus on, as part of its work on this topic going forward.
- Review whether any outputs from the HFEA are required, to address the use, or regulation, of AI, robotics and automation in fertility treatment.

14. Annex A: Application of the HFEA Code of Practice to AI, robotics and automation

The following parts of the HFEA Code of Practice provide examples of how the HFEA applies our existing regulatory framework to regulate the use of AI, robotics and automation in fertility clinics:

14.1. Guidance note 18, "witnessing and assuring patient and donor identification", states that "centres must have in place robust and effective processes to ensure that no mismatches of gametes or embryos or identification errors occur."

14.2. Guidance note 23, "the quality management system" states that "required standards of quality and safety, in the form of quality indicators for all activities authorised by this licence and other activities carried out in the course of providing treatment services that do not require a licence, must be established."

14.3. Guidance note 23 also states that "centres must audit the activities and processes authorised by this licence and other activities carried out in the course of providing treatment services that do not require a licence against compliance with the regulatory requirements and their own approved protocols and quality indicators. These audits must be performed at least every two years, by trained and competent staff and in an independent way. Findings and corrective actions must be documented and implemented."

14.4. Guidance note 27, "adverse incidents", states that "centre must establish, implement and comply with documented procedures to report, investigate, register and transmit information about serious adverse events and serious adverse reactions that occur"

15. References

Acker A, Senapati S, Dokras A. Barriers to access: findings from an implementation study of an artificial intelligence-augmented 2-way chatbot for fertility care. *Fertil Steril* [Internet] 2023;**120**:199–201. Elsevier Inc.

Ahlström A, Berntsen J, Johansen M, Bergh C, Cimadomo D, Hardarson T, Lundin K. Correlations between a deep learning-based algorithm for embryo evaluation with cleavage-stage cell numbers and fragmentation. *Reprod Biomed Online* 2023;**47**:. Elsevier Ltd.

Amitai T, Kan-Tor Y, Or Y, Shoham Z, Shofaro Y, Richter D, Har-Vardi I, Ben-Meir A, Srebnik N, Buxboim A. Embryo classification beyond pregnancy: early prediction of first trimester miscarriage using machine learning. *J Assist Reprod Genet* 2023;**40**:309–322. Springer.

Awad S, Aljuburi L, Lumsden RS, Mpandzou M, Marinus R. Connected health in US, EU, and China: opportunities to accelerate regulation of connected health technologies to optimize their role in medicines development. *Front Med (Lausanne)* [Internet] 2023;**10**:1248912. Frontiers Media SA.

Bachelot G, Dhombres F, Sermondade N, Hamid RH, Berthaut I, Frydman V, Prades M, Kolanska K, Selleret L, Mathieu-D'Argent E, *et al.* A Machine Learning Approach for the Prediction of Testicular Sperm Extraction in Nonobstructive Azoospermia: Algorithm Development and Validation Study. *J Med Internet Res* 2023;**25**:. JMIR Publications Inc.

Bamford T, Easter C, Montgomery S, Smith R, Dhillon-Smith RK, Barrie A, Campbell A, Coomarasamy A. A comparison of 12 machine learning models developed to predict ploidy, using a morphokinetic meta-dataset of 8147 embryos. *Human Reproduction* 2023;**38**:569–581. Oxford University Press.

Barnes J, Brendel M, Gao VR, Rajendran S, Kim J, Li Q, Malmsten JE, Sierra JT, Zisimopoulos P, Sigaras A, *et al.* A non-invasive artificial intelligence approach for the prediction of human blastocyst ploidy: a retrospective model development and validation study. *Lancet Digit Health* 2023;**5**:e28–e40. Elsevier Ltd.

Bockting CL, Dis EAAM van, Rooij R van, Zuidema W, Bollen J. Living guidelines for generative AI — why scientists must oversee its use. *Nature 2023 622:7984* [Internet] 2023;**622**:693–696. Nature Publishing Group.

Bristows LLP. Issue 11 of the Year Biotech Review. 2023;

Buldo-Licciardi J, Large MJ, McCulloh DH, McCaffrey C, Grifo JA. Utilization of standardized preimplantation genetic testing for aneuploidy (PGT-A) via artificial intelligence (AI) technology is correlated with improved pregnancy outcomes in single thawed euploid embryo transfer (STEET) cycles. *J Assist Reprod Genet* 2023;**40**:289–299. Springer.

Čapek D, Safroshkin M, Morales-Navarrete H, Toulany N, Arutyunov G, Kurzbach A, Bihler J, Hagauer J, Kick S, Jones F, *et al.* EmbryoNet: using deep learning to link embryonic phenotypes to signaling pathways. *Nat Methods* 2023;**20**:815–823. Nature Research.

Charnpinyo N, Suthicharoenpanich K, Onthuam K, Engphaiboon S, Chaichaowarat R, Suebthawinkul C, Siricharoen P. Embryo Selection for IVF using Machine Learning Techniques Based on Light Microscopic Images of Embryo and Additional Factors. *Annu Int Conf IEEE Eng Med Biol Soc* [Internet] 2023;**2023**:1–4. Annu Int Conf IEEE Eng Med Biol Soc.

Chen F, Xie X, Cai D, Yan P, Ding C, Wen Y, Xu Y, Gao F, Zhou C, Li G, *et al.* Knowledge-embedded spatio-temporal analysis for euploidy embryos identification in couples with chromosomal rearrangements. *Chin Med J (Engl)* [Internet] 2023a;. Ovid Technologies (Wolters Kluwer Health)Available from: http://www.ncbi.nlm.nih.gov/pubmed/37640743.

Chen RJ, Wang JJ, Williamson DFK, Chen TY, Lipkova J, Lu MY, Sahai S, Mahmood F. Algorithmic fairness in artificial intelligence for medicine and healthcare. *Nat Biomed Eng* [Internet] 2023b;**7**:719–742. NLM (Medline).

Cheredath A, Uppangala S, Asha CS, Jijo A, Vani Lakshmi R, Kumar P, Joseph D, Nagana NG, Kalthur G, Adiga SK. Combining Machine Learning with Metabolomic and Embryologic Data Improves Embryo Implantation Prediction. *Reproductive Sciences* 2023;**30**:984–994. Institute for Ionics.

Cherouveim P, Jiang VS, Kanakasabapathy MK, Thirumalaraju P, Souter I, Dimitriadis I, Bormann CL, Shafiee H. Quality assurance (QA) for monitoring the performance of assisted reproductive technology (ART) staff using artificial intelligence (AI). *J Assist Reprod Genet* 2023a;**40**:241–249. Springer.

Cherouveim P, Velmahos C, Bormann CL. Artificial intelligence for sperm selection—a systematic review. *Fertil Steril* 2023b;**120**:24–31. Elsevier Inc.

Coghlan S, Gyngell C, Vears DF. Ethics of artificial intelligence in prenatal and pediatric genomic medicine. *J Community Genet* [Internet] 2023;**1**:1–12. Springer Science and Business Media Deutschland GmbH.

Costa-Borges N, Munné S, Albó E, Mas S, Castelló C, Giralt G, Lu Z, Chau C, Acacio M, Mestres E, *et al.* First babies conceived with Automated Intracytoplasmic Sperm Injection. *Reprod Biomed Online* [Internet] 2023;**47**:103237. Elsevier Ltd.

Council of the EU. Artificial intelligence act: Council and Parliament strike a deal on the first rules for AI in the world - Consilium. 2023;Available from: https://www.consilium.europa.eu/en/press/press-releases/2023/12/09/artificial-intelligence-act-council-and-parliament-strike-a-deal-on-the-first-worldwide-rules-for-ai/.

Curchoe CL. Proceedings of the first world conference on AI in fertility. *J Assist Reprod Genet* [Internet] 2023a;**40**:215–222. Springer.

Curchoe CL. Unlock the algorithms: regulation of adaptive algorithms in reproduction. *Fertil Steril* [Internet] 2023b;**120**:38–43. Elsevier Inc.

Curchoe CL, Bormann C, Hammond E, Salter S, Timlin C, Williams LB, Gilboa D, Seidman D, Campbell A, Morbeck D. Assuring quality in assisted reproduction laboratories: assessing the performance of ART Compass — a digital art staff management platform. *J Assist Reprod Genet* [Internet] 2023a;**40**:265–278. Springer.

Curchoe CL, Letterie GS, Quaas AM. Unlocking the potential of artificial intelligence (AI) in reproductive medicine: the JARG collection on assisted reproductive technology (ART) and machine learning. *J Assist Reprod Genet* [Internet] 2023b;**40**:2079–2080. Springer.

Farias AFS, Chavez-Badiola A, Mendizabal-Ruiz G, Valencia-Murillo R, Drakeley A, Cohen J, Cardenas-Esparza E. Automated identification of blastocyst regions at different development stages. *Sci Rep* 2023;**13**:. Nature Research.

Fruchter-Goldmeier Y, Kantor B, Ben-Meir A, Wainstock T, Erlich I, Levitas E, Shufaro Y, Sapir O, Har-Vardi I. An artificial intelligence algorithm for automated blastocyst morphometric parameters demonstrates a positive association with implantation potential. *Sci Rep* 2023;**13**:. Nature Research.

Garcia-Grau E, Oliveira M, Amengual MJ, Rodriguez-Sanchez E, Veraguas-Imbernon A, Costa L, Benet J, Ribas-Maynou J. An Algorithm to Predict the Lack of Pregnancy after Intrauterine Insemination in Infertile Patients. *J Clin Med* [Internet] 2023;**12**:. Multidisciplinary Digital Publishing Institute (MDPI).

Ghayda RA, Cannarella R, Calogero AE, Shah R, Rambhatla A, Zohdy W, Kavoussi P, Avidor-Reiss T, Boitrelle F, Mostafa T, *et al.* Artificial Intelligence in Andrology: From Semen Analysis to Image Diagnostics. *World J Mens Health* [Internet] 2023;**41**:. XMLink.

GhoshRoy D, Alvi PA, Santosh K. AI Tools for Assessing Human Fertility Using Risk Factors: A State-of-the-Art Review. *J Med Syst* [Internet] 2023a;**47**:91. Springer.

GhoshRoy D, Alvi PA, Santosh KC. Unboxing Industry-Standard AI Models for Male Fertility Prediction with SHAP. *Healthcare (Basel)* [Internet] 2023b;**11**:. MDPI.

Gill ME, Quaas AM. Looking with new eyes: advanced microscopy and artificial intelligence in reproductive medicine. *J Assist Reprod Genet* [Internet] 2023;**40**:235–239. Springer.

Glatstein I, Chavez-Badiola A, Curchoe CL. New frontiers in embryo selection. *J Assist Reprod Genet* [Internet] 2023;**40**:223–234. Springer.

Go KJ, Hudson C. Deep technology for the optimization of cryostorage. *J Assist Reprod Genet* [Internet] 2023;**40**:1829–1834. Springer.

Grayek E, Krishnamurti T, Hu L, Babich O, Warren K, Fischhoff B. Collection and Analysis of Adherence Information for Software as a Medical Device Clinical Trials: Systematic Review. *JMIR Mhealth Uhealth* [Internet] 2023;**11**:e46237. JMIR Mhealth Uhealth.

Güell E. Criteria for implementing artificial intelligence systems in reproductive medicine. *Clin Exp Reprod Med* [Internet] 2023; Clin Exp Reprod MedAvailable from: https://pubmed.ncbi.nlm.nih.gov/38035589/.

Hardman D, Bennett RD, Mikhail E. Fertility sparing double discoid excision of rectosigmoid deep endometriosis under robotic-integrated ultrasound guidance. *Fertil Steril* [Internet] 2024;**121**:. Fertil Steril.

Hariton E, Pavlovic Z, Fanton M, Jiang VS. Applications of artificial intelligence in ovarian stimulation: a tool for improving efficiency and outcomes. *Fertil Steril* [Internet] 2023;**120**:8–16. Elsevier Inc.

Hengstschläger M. Artificial intelligence as a door opener for a new era of human reproduction. *Hum Reprod Open* [Internet] 2023;**2023**:. Hum Reprod Open.

Ho CWL. Implementing the human right to science in the regulatory governance of artificial intelligence in healthcare. *J Law Biosci* [Internet] 2023;**10**:lsad026.

Horta F, Salih M, Austin C, Warty R, Smith V, Rolnik DL, Reddy S, Rezatofighi H, Vollenhoven B. Reply: Artificial intelligence as a door opener for a new era of human reproduction. *Hum Reprod Open* [Internet] 2023;**2023**:. Hum Reprod Open.

Houri O, Gil Y, Danieli-Gruber S, Shufaro Y, Sapir O, Hochberg A, Ben-Haroush A, Wertheimer A. Prediction of oocyte maturation rate in the GnRH antagonist flexible IVF protocol using a novel machine learning algorithm – A retrospective study. *European Journal of Obstetrics and Gynecology and Reproductive Biology* 2023;**284**:100–104. Elsevier Ireland Ltd.

Hsu CT, Lee CI, Huang CC, Wang TE, Chang HC, Chang LS, Lee MS. Development and integration of LensHooke® R10 for automatic and standardized diagnosis for sperm DNA fragmentation. *Andrology* 2023; John Wiley and Sons Inc.

Huang H-H, Hsieh S-J, Chen M-S, Jhou M-J, Liu T-C, Shen H-L, Yang C-T, Hung C-C, Yu Y-Y, Lu C-J. Machine Learning Predictive Models for Evaluating Risk Factors Affecting Sperm Count: Predictions Based on Health Screening Indicators. *J Clin Med* [Internet] 2023a;**12**:. MDPI.

Huang H-H, Lu C-J, Jhou M-J, Liu T-C, Yang C-T, Hsieh S-J, Yang W-J, Chang H-C, Chen M-S. Using a Decision Tree Algorithm Predictive Model for Sperm Count Assessment and Risk Factors in Health Screening Population. *Risk Manag Healthc Policy* [Internet] 2023b;**16**:2469–2478. Risk Manag Healthc Policy.

Information Commissioner's Office. ICO to review period and fertility tracking apps as poll shows more than half of women are concerned over data security. *ICO News* [Internet] 2023; ICOAvailable from: https://ico.org.uk/about-the-ico/media-centre/news-and-blogs/2023/09/ico-to-review-period-and-fertility-tracking-apps/.

Jiang VS, Bormann CL. Artificial intelligence in the in vitro fertilization laboratory: a review of advancements over the last decade. *Fertil Steril* 2023a;**120**:17–23. Elsevier Inc.

Jiang VS, Bormann CL. Noninvasive genetic screening: current advances in artificial intelligence for embryo ploidy prediction. *Fertil Steril* 2023b;**120**:228–234. Elsevier Inc.

Jiang VS, Kandula H, Thirumalaraju P, Kanakasabapathy MK, Cherouveim P, Souter I, Dimitriadis I, Bormann CL, Shafiee H. The use of voting ensembles to improve the accuracy of deep neural networks as a non-invasive method to predict embryo ploidy status. *J Assist Reprod Genet* [Internet] 2023a;**40**:301–308. Springer.

Jiang VS, Kartik D, Thirumalaraju P, Kandula H, Kanakasabapathy MK, Souter I, Dimitriadis I, Bormann CL, Shafiee H. Advancements in the future of automating micromanipulation techniques in the IVF laboratory using deep convolutional neural networks. *J Assist Reprod Genet* 2023b;**40**:251–257. Springer.

Jiang VS, Pavlovic ZJ, Hariton E. The Role of Artificial Intelligence and Machine Learning in Assisted Reproductive Technologies. *Obstet Gynecol Clin North Am* [Internet] 2023c;**50**:747–762.

Jin W, Lin J, Wang P, Yang H, Jin C. Screening the predictors for live birth failure in women after the first frozen embryo transfer based on the Lasso algorithm: a retrospective study. *Zygote* 2023;**31**:350–358. NLM (Medline).

Johansen MN, Parner ET, Kragh MF, Kato K, Ueno S, Palm S, Kernbach M, Balaban B, Keleş İ, Gabrielsen A V., *et al.* Comparing performance between clinics of an embryo evaluation algorithm based on time-lapse images and machine learning. *J Assist Reprod Genet* 2023;**40**:2129–2137. Springer.

Kharb S, Joshi A. Multi-omics and machine learning for the prevention and management of female reproductive health. *Front Endocrinol (Lausanne)* 2023;**14**:. Frontiers Media S.A.

Kim SJ, Park MH, Lee JH. Comparison of operative and fertility outcomes of single-incision robotic myomectomy: a retrospective single-center analysis of 286 cases. *J Robot Surg* 2023; Springer Nature.

Kondow A, Ohnuma K, Taniguchi A, Sakamoto J, Asashima M, Kato K, Kamei Y, Nonaka S. Automated contour extraction for light-sheet microscopy images of zebrafish embryos based on object edge detection algorithm. *Dev Growth Differ* 2023;**65**:311–320. John Wiley and Sons Inc.

Kromp F, Wagner R, Balaban B, Cottin V, Cuevas-Saiz I, Schachner C, Fancsovits P, Fawzy M, Fischer L, Findikli N, *et al.* An annotated human blastocyst dataset to benchmark deep learning architectures for in vitro fertilization. *Sci Data* 2023;**10**:. Nature Research.

Kumar RS, Sharma S, Halder A, Gupta V. Deep Learning-Based Robust Automated System for Predicting Human Sperm DNA Fragmentation Index. *J Hum Reprod Sci* [Internet] 2023;**16**:16–21. Medknow.

Kuroda S, Karna KK, Kaiyal RS, Cannarella R, Lundy SD, Vij SC, Agarwal A. Novel sperm chromatin dispersion test with artificial intelligence-aided halo evaluation: A comparison study with existing modalities. *Andrology* 2023; John Wiley and Sons Inc.

Lee JH, Park SY, Jeong K, Yun HY, Chung HW. What is the role of robotic surgery in ovarian cystectomy with fertility preservation? *J Robot Surg* 2023a;. Springer Nature.

Lee T, Natalwala J, Chapple V, Liu Y. A brief history of artificial intelligence embryo selection: from black-box to glass-box. *Hum Reprod* [Internet] 2023b;. Hum ReprodAvailable from: https://pubmed.ncbi.nlm.nih.gov/38061074/.

Lee VV, Vijayakumar S, Ng WY, Lau NY, Leong QY, Ooi DSQ, Su LL, Lee YS, Chan SY, Blasiak A, *et al.* Personalization and localization as key expectations of digital health intervention in women pre- to post-pregnancy. *NPJ Digit Med* 2023c;**6**:. Nature Research.

Lenharo M. An AI revolution is brewing in medicine. What will it look like? *Nature* [Internet] 2023;**622**:686–688. Nature Research.

Letterie G. Artificial intelligence and assisted reproductive technologies: 2023. Ready for prime time? Or not. *Fertil Steril* [Internet] 2023;**120**:32–37. Elsevier Inc.

Li L, Cui X, Yang J, Wu X, Zhao G. Using feature optimization and LightGBM algorithm to predict the clinical pregnancy outcomes after in vitro fertilization. *Front Endocrinol (Lausanne)* [Internet] 2023a;**14**:. Front Endocrinol (Lausanne).

Li T, Liao R, Chan C, Greenblatt EM. Deep learning analysis of endometrial histology as a promising tool to predict the chance of pregnancy after frozen embryo transfers. *J Assist Reprod Genet* 2023b;**40**:901–910. Springer.

Liang X, He J, He L, Lin Y, Li Y, Cai K, Wei J, Lu Y, Chen Z. An ultrasound-based deep learning radiomic model combined with clinical data to predict clinical pregnancy after frozen embryo transfer: a pilot cohort study. *Reprod Biomed Online* 2023;**47**:. Elsevier Ltd.

Ling S, Blackburn BJ, Jenkins MW, Watanabe M, Ford SM, Lapierre-Landry M, Rollins AM. Segmentation of beating embryonic heart structures from 4-D OCT images using deep learning. *Biomed Opt Express* [Internet] 2023;**14**:1945–1958. Optica Publishing Group.

Liu H, Zhang Z, Gu Y, Dai C, Shan G, Song H, Li D, Chen W, Lin G, Sun Y. Development and evaluation of a live birth prediction model for evaluating human blastocysts from a retrospective study. *Elife* [Internet] 2023a;**12**:. Elife.

Liu X, Chen Z, Ji Y. Construction of the machine learning-based live birth prediction models for the first in vitro fertilization pregnant women. *BMC Pregnancy Childbirth* 2023b;**23**:. BioMed Central Ltd.

Louis CM, Handayani N, Aprilliana T, Polim AA, Boediono A, Sini I. Genetic algorithm-assisted machine learning for clinical pregnancy prediction in in vitro fertilization. *AJOG global reports* [Internet] 2023;**3**:100133. Elsevier Inc.

Luigi-Bravo G, Maria Ramirez A, Gerdts C, Gill R. Lessons learned from developing and implementing digital health tools for self-managed abortion and sexual and reproductive healthcare in Canada, the United States, and Venezuela. *Sex Reprod Health Matters* [Internet] 2023;**31**:2266305. Taylor and Francis Ltd.

Lustgarten Guahmich N, Borini E, Zaninovic N. Improving outcomes of assisted reproductive technologies using artificial intelligence for sperm selection. *Fertil Steril* [Internet] 2023;**120**:729–734. Elsevier Inc.

Mahali MI, Leu JS, Darmawan JT, Avian C, Bachroin N, Prakosa SW, Faisal M, Putro NAS. A Dual Architecture Fusion and AutoEncoder for Automatic Morphological Classification of Human Sperm. *Sensors* 2023;**23**:. Multidisciplinary Digital Publishing Institute (MDPI).

Majumdar G, Sengupta A, Narad P, Pandey H. Deep Inception-ResNet: A Novel Approach for Personalized Prediction of Cumulative Pregnancy Outcomes in Vitro Fertilization Treatment (IVF). *Journal of Obstetrics and Gynecology of India* [Internet] 2023;**73**:343–350. Springer.

Malin-Mayor C, Hirsch P, Guignard L, McDole K, Wan Y, Lemon WC, Kainmueller D, Keller PJ, Preibisch S, Funke J. Automated reconstruction of whole-embryo cell lineages by learning from sparse annotations. *Nat Biotechnol* 2023;**41**:44–49. Nature Research.

Miloski B. Opportunities for artificial intelligence in healthcare and in vitro fertilization. *Fertil Steril* [Internet] 2023;**120**:3–7. Elsevier Inc.

Nadarzynski T, Lunt A, Knights N, Bayley J, Llewellyn C. “But can chatbots understand sex?” Attitudes towards artificial intelligence chatbots amongst sexual and reproductive health professionals: An exploratory mixed-methods study. *Int J STD AIDS* [Internet] 2023;**34**:809–816. SAGE Publications Ltd.

Noy L, Barnea I, Mirsky SK, Kamber D, Levi M, Shaked NT. Sperm-cell DNA fragmentation prediction using label-free quantitative phase imaging and deep learning. *Cytometry Part A* 2023;**103**:470–478. John Wiley and Sons Inc.

Ozer G, Akca A, Yuksel B, Duzguner I, Pehlivanli AC, Kahraman S. Prediction of risk factors for first trimester pregnancy loss in frozen-thawed good-quality embryo transfer cycles using machine learning algorithms. *J Assist Reprod Genet* 2023;**40**:279–288. Springer.

Palmer GA, Tomkin G, Martín-Alcalá HE, Mendizabal-Ruiz G, Cohen J. The Internet of Things in assisted reproduction. *Reprod Biomed Online* [Internet] 2023;**47**:103338. Elsevier BV.

Parrella A, Rubio Riquelme N, Os Galdos LA Van, Vilella Amorós I, Jiménez Gadea M, Aizpurua J. P-110 A novel Artificial Intelligence Microscopy: Mojo AISA, the new way to perform semen analysis. *Human Reproduction* 2022;**37**:. Oxford University Press (OUP).

Peng T, Liao C, Ye X, Chen Z, Li X, Lan Y, Fu X, An G. Machine learning-based clustering to identify the combined effect of the DNA fragmentation index and conventional semen parameters on in vitro fertilization outcomes. *Reproductive Biology and Endocrinology* 2023;**21**:. BioMed Central Ltd.

Rolfe SM, Whikehart SM, Maga AM. Deep learning enabled multi-organ segmentation of mouse embryos. *Biol Open* [Internet] 2023;**12**:. The Company of Biologists.

Rolfes V, Bittner U, Gerhards H, Krüssel J-S, Fehm T, Ranisch R, Fangerau H. Artificial Intelligence in Reproductive Medicine - An Ethical Perspective. *Geburtshilfe Frauenheilkd* [Internet] 2023;**83**:106–115. Georg Thieme Verlag.

Salih M, Austin C, Warty RR, Tiktin C, Rolnik DL, Momeni M, Rezatofighi H, Reddy S, Smith V, Vollenhoven B, *et al.* Embryo selection through artificial intelligence versus embryologists: a systematic review. *Hum Reprod Open* [Internet] 2023;**2023**:hoad031. Oxford University Press (OUP).

Semrl N, Feigl S, Taumberger N, Bracic T, Fluhr H, Blockeel C, Kollmann M. AI language models in human reproduction research: exploring ChatGPT's potential to assist academic writing. *Human Reproduction* [Internet] 2023;Available from: https://academic.oup.com/humrep/advance-article/doi/10.1093/humrep/dead207/7313666.

Sengupta P, Dutta S, Roychoudhury S, Vizzarri F, Slama P. Revolutionizing semen analysis: introducing Mojo AISA, the next-gen artificial intelligence microscopy. *Front Cell Dev Biol* [Internet] 2023;**11**:1203708. Frontiers Media SA.

Serdarogullari M, Raad G, Yarkiner Z, Bazzi M, Mourad Y, Alpturk S, Fakih F, Fakih C, Liperis G. Identifying predictors of Day 5 blastocyst utilization rate using an artificial neural network. *Reprod Biomed Online* [Internet] 2023;**47**:103399. Elsevier BV.

Shea AA, Thornburg J, Vitzthum VJ. Assessment of App-Based Versus Conventional Survey Modalities for Reproductive Health Research in India, South Africa, and the United States: Comparative Cross-Sectional Study. *JMIR Form Res* [Internet] 2023;**7**:e44705. JMIR Form Res.

Si K, Huang B, Jin L. Application of artificial intelligence in gametes and embryos selection. *Hum Fertil (Camb)* [Internet] 2023;1–21. Taylor and Francis Ltd.Available from: http://www.ncbi.nlm.nih.gov/pubmed/37705466.

Sparidaens EM, Logger JGM, Nelen WLDM, Braat DDM, Fleischer K, Hermens RPM. Web-based Guidance for Assisted Reproductive Technology with an Online App (myFertiCare): Quantitative Evaluation with the HOT-fit Framework. *J Med Internet Res* 2023;**25**:. JMIR Publications Inc.

Strawbridge SE, Kurowski A, Corujo-Simon E, Fletcher AN, Nichols J, Fletcher AG. insideOutside: an accessible algorithm for classifying interior and exterior points, with applications in embryology. *Biol Open* [Internet] 2023;**12**:. The Company of Biologists.

The Lancet Digital Health. Enhancing the success of IVF with artificial intelligence. *Lancet Digit Health* [Internet] 2023;**5**:e1. Elsevier Ltd.

Theilgaard Lassen J, Fly Kragh M, Rimestad J, Nygård Johansen M, Berntsen J. Development and validation of deep learning based embryo selection across multiple days of transfer. *Sci Rep* [Internet] 2023;**13**:4235. Nature Research.

Tran HP, Diem Tuyet HT, Dang Khoa TQ, Lam Thuy LN, Bao PT, Thanh Sang VN. Microscopic Video-Based Grouped Embryo Segmentation: A Deep Learning Approach. *Cureus* [Internet] 2023;**15**:e45429. Springer Science and Business Media LLC.

Ueno S, Berntsen J, Okimura T, Kato K. Improved pregnancy prediction performance in an updated deep-learning embryo selection model: a retrospective independent validation study. *Reprod Biomed Online* [Internet] 2023;103308. Elsevier BVAvailable from: http://www.ncbi.nlm.nih.gov/pubmed/37914559.

Valera MA, Aparicio-Ruiz B, Pérez-Albalá S, Romany L, Remohí J, Meseguer M. Clinical validation of an automatic classification algorithm applied on cleavage stage embryos: analysis for blastulation, euploidy, implantation, and live-birth potential. *Human Reproduction* 2023;**38**:1060–1075. Oxford University Press.

Veiga M, Camia B, Diepenbrock S, Redi C, Casasco A, Monti M. Artificial intelligence selection of viable oocytes from phase contrast images for in vitro maturation and fertilization. *Biol Reprod* [Internet] 2023;**109**:386–389. Oxford University Press (OUP).

Wang R, Pan W, Yu L, Zhang X, Pan W, Hu C, Wen L, Jin L, Liao S. AI-Based Optimal Treatment Strategy Selection for Female Infertility for First and Subsequent IVF-ET Cycles. *J Med Syst* 2023a;**47**:. Springer.

Wang S, Chen L, Sun H. Interpretable artificial intelligence assisted embryo selection improved single blastocyst transfer outcomes: a prospective cohort study. *Reprod Biomed Online* 2023b;103371. Elsevier BV.

Watson A, Chapman R, Shafai G, Maricich YA. FDA regulations and prescription digital therapeutics: Evolving with the technologies they regulate. *Front Digit Health* [Internet] 2023;**5**:1086219. Frontiers Media S.A.

Welzel C, Cotte F, Wekenborg M, Vasey B, McCulloch P, Gilbert S. Holistic Human-Serving Digitization of Health Care Needs Integrated Automated System-Level Assessment Tools. *J Med Internet Res* [Internet] 2023;**25**:e50158. J Med Internet Res.

World Health Organisation (WHO). WHO calls for safe and ethical AI for health. *WHO News* [Internet] 2023;Available from: https://www.who.int/news/item/16-05-2023-who-calls-for-safe-and-ethical-ai-for-health.

www.digitalregulations.innovation.nhs.uk. AI and Digital Regulations Service for health and social care - AI regulation service - NHSAvailable from: https://www.digitalregulations.innovation.nhs.uk/.

www.gov.uk. AI regulation: a pro-innovation approach. *White Paper* [Internet] 2023a;Available from: https://www.gov.uk/government/publications/ai-regulation-a-pro-innovation-approach.

www.gov.uk. Pro-innovation Regulation of Technologies Review Cross-cutting and Growth Duty Recommendations. 2023b;.

www.gov.uk. Pro-innovation Regulation of Technologies Review-Cross Cutting-HMG Response 1 HM Government Response to Professor Dame Angela McLean's Pro-Innovation Regulation of Technologies Review Cross Cutting. 2023c;.

www.gov.uk. AI Safety Summit 2023: Roundtable Chairs' Summaries, 1 November - GOV.UK. *AI Safety Summit* [Internet] 2023d;Available from: https://www.gov.uk/government/publications/ai-safety-

summit-1-november-roundtable-chairs-summaries/ai-safety-summit-2023-roundtable-chairs-summaries-1-november--2.

www.gov.uk. AI Safety Summit 2023: Roundtable Chairs' Summaries, 2 November - GOV.UK. *AI Safety Summit* [Internet] 2023e;Available from: https://www.gov.uk/government/publications/ai-safety-summit-2023-roundtable-chairs-summaries-2-november/ai-safety-summit-2023-roundtable-chairs-summaries-2-november.

www.gov.uk. Countries agree to safe and responsible development of frontier AI in landmark Bletchley Declaration - GOV.UK. *Press release* [Internet] 2023f;Available from: https://www.gov.uk/government/news/countries-agree-to-safe-and-responsible-development-of-frontier-ai-in-landmark-bletchley-declaration.

www.gov.uk. Introducing the AI Safety Institute - GOV.UK. *AI Safety Summit* [Internet] 2023g;Available from: https://www.gov.uk/government/publications/ai-safety-institute-overview/introducing-the-ai-safety-institute.

www.gov.uk. New innovation challenge launched to tackle bias in AI systems - GOV.UK. *Press release* [Internet] 2023h;Available from: https://www.gov.uk/government/news/new-innovation-challenge-launched-to-tackle-bias-in-ai-systems.

www.gov.uk. New £100 million fund to capitalise on AI's game-changing potential in life sciences and healthcare - GOV.UK. *Press release* [Internet] 2023i;Available from: https://www.gov.uk/government/news/new-100-million-fund-to-capitalise-on-ais-game-changing-potential-in-life-sciences-and-healthcare.

www.gov.uk. Software and AI as a Medical Device Change Programme - Roadmap - GOV.UK. *Medicines and Healthcare products Regulatory Agency* [Internet] 2023j;Available from: https://www.gov.uk/government/publications/software-and-ai-as-a-medical-device-change-programme/software-and-ai-as-a-medical-device-change-programme-roadmap.

www.gov.uk. MHRA to launch the AI-Airlock, a new regulatory sandbox for AI developers - GOV.UK. *Medicines and Healthcare products Regulatory Agency* [Internet] 2023k;Available from: https://www.gov.uk/government/news/mhra-to-launch-the-ai-airlock-a-new-regulatory-sandbox-for-ai-developers.

www.gov.uk. Algorithmic Transparency Recording Standard Hub - GOV.UK. *Collection* [Internet] 2023l;Available from: https://www.gov.uk/government/collections/algorithmic-transparency-recording-standard-hub.

www.publications.parliament.uk. Lack of AI-specific legislation in King's Speech risks UK ambitions. *News* [Internet] 2023a;Available from: https://committees.parliament.uk/work/6986/governance-of-artificial-intelligence-ai/news/198315/lack-of-aispecific-legislation-in-kings-speech-risks-uk-ambitions/.

www.publications.parliament.uk. The governance of artificial intelligence: interim report - Science, Innovation and Technology Committee. *House of Commons Committee report* [Internet] 2023b;Available from: https://publications.parliament.uk/pa/cm5803/cmselect/cmsctech/1769/report.html.

www.publications.parliament.uk. The governance of artificial intelligence: interim report: Government response to the Committee's Ninth report - Science, Innovation and Technology Committee. *House of Commons Science, Innovation and Technology Committee* [Internet] 2023c;Available from: https://publications.parliament.uk/pa/cm5804/cmselect/cmsctech/248/report.html.

Wyatt JC, Scott P, Ordish J, South M, Thomas M, Jones C, Lacey-Bryant S, workshop participants. Which computable biomedical knowledge objects will be regulated? Results of a UK workshop discussing

the regulation of knowledge libraries and software as a medical device. *Learn Health Syst* [Internet] 2023;**7**:e10386. John Wiley and Sons Inc.

Youngster M, Luz A, Baum M, Hourvitz R, Reuvenny S, Maman E, Hourvitz A. Artificial intelligence in the service of intrauterine insemination and timed intercourse in spontaneous cycles. *Fertil Steril* 2023; Elsevier Inc.

Yu J, Zhang J, Sengoku S. Innovation Process and Industrial System of US Food and Drug Administration-Approved Software as a Medical Device: Review and Content Analysis. *J Med Internet Res* [Internet] 2023;**25**:. J Med Internet Res.

Yuan Z, Yuan M, Song X, Huang X, Yan W. Development of an artificial intelligence based model for predicting the euploidy of blastocysts in PGT-A treatments. *Sci Rep* 2023;**13**:. Nature Research.

Zabari N, Kan-Tor Y, Or Y, Shoham Z, Shufaro Y, Richter D, Har-Vardi I, Ben-Meir A, Srebnik N, Buxboim A. Delineating the heterogeneity of embryo preimplantation development using automated and accurate morphokinetic annotation. *J Assist Reprod Genet* 2023;**40**:1391–1406. Springer.

Zaninovic N, Sierra ET, Malmsten JE, Rosenwaks Z. Embryo ranking agreement between embryologists and artificial intelligence (AI) algorithms. *F S Sci* [Internet] 2023;Available from: http://www.ncbi.nlm.nih.gov/pubmed/37820865.

Zhao J, Bai C, Zhang Z, Zhang Q. Deep learning-based method for analyzing the optically trapped sperm rotation. *Sci Rep* 2023;**13**:. Nature Research.

Zheng Z, Wang Y, Ni N, Tong G, Cheng N, Yin P, Chen Y, Wu Y, Xie G, Yang T. Deep Learning-Based Quantitative Blastocyst Assessment. *Annu Int Conf IEEE Eng Med Biol Soc* [Internet] 2023;**2023**:1–4. Annu Int Conf IEEE Eng Med Biol Soc.

Zhu J, Wu L, Liu J, Liang Y, Zou J, Hao X, Huang G, Han W. External validation of a model for selecting day 3 embryos for transfer based upon deep learning and time-lapse imaging. *Reprod Biomed Online* 2023a;**47**:. Elsevier Ltd.

Zhu Y, Feng HL, Jiang MX. Evaluation of an automated dish preparation system for IVF and embryo culture using a mouse mode. *Sci Rep* 2023b;**13**:16490. NLM (Medline).

Zhu Y, Zhang Q-J, Feng HL, Luo J, Miao S, Jiang M-X. Automation in vitrification and thawing of mouse oocytes and embryos. *Front Cell Dev Biol* [Internet] 2023c;**11**:. Front Cell Dev Biol.