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

Wednesday 3rd June 2026

Date	Action	Responsibility	Due date	Progress to date
04/02/2026	Bring the discussion on the topic of 'Germline/heritable genome editing' forward in the workplan so that any new publications can be discussed in a timely manner.	Rebecca Taylor, Scientific Policy Manager	03/06/2026	Discussion to be brought forward as needed.
04/02/2026	Move the topic of 'Understanding the genetic basis of infertility' from the watching brief list to medium priority.	Rebecca Taylor, Scientific Policy Manager	03/06/2026	Actioned.
04/02/2026	Split topic of 'Reproductive organoids' into 'Female reproductive organoids' and 'Male reproductive organoids'.	Mina Mincheva, Policy Manager	03/06/2026	Actioned. Relevant search terms will be updated.
04/02/2026	Split topic of 'Artificial intelligence, robotics and automation in fertility treatment' into 'AI in fertility treatment' and 'Robotics and automation in fertility treatment'.	Mina Mincheva, Policy Manager	03/06/2026	Actioned. Relevant search terms will be updated.

Emerging technologies in embryo and gamete testing

Details about this paper

Area(s) of strategy this paper relates to:	Supporting scientific and medical innovation
Meeting:	Scientific and Clinical Advances Advisory Committee (SCAAC)
Agenda item:	5
Paper number:	HFEA (03/06/2026) 005
Meeting date:	03 June 2026
Author:	Mina Mincheva, Policy Manager (HFEA)
Annexes	Annex A – Literature review and scope of Emerging technologies in embryo and gamete testing

Output from this paper

For information or recommendation?	For recommendation
Recommendation:	Members are asked to: • Consider the progress of research into embryo and gamete testing; • Advise the Executive if they are aware of any other recent developments; • Review whether any outputs from the HFEA are required addressing the use of emerging technologies in embryo and gamete testing.
Resource implications:	Within budget
Implementation date:	N/A
Communication(s):	Minutes of the committee discussion will be published on the SCAAC webpage and communicated to the sector via our Clinic Focus newsletter.
Organisational risk:	Low

1. Background

1.1. Preimplantation genetic testing (PGT) for embryos allows the testing for hereditary genetic disorders and chromosome abnormalities in embryos before implantation.

1.2. The **Human Fertilisation and Embryology Act 1990 (as amended)** (the HFE Act) prohibits embryo testing except for one or more of the purposes expressly permitted in **paragraph 1ZA(1) of Schedule 2 of the Act**.

1.3. Embryos can only be selected for transfer based on information from testing that meets a specified purpose in law. Clinics must adhere to Standard Licence Conditions: T86-T91, summarised as follows:

- Embryos that are known to have a genetic abnormality which presents a significant risk that the child will have a serious condition must not be preferred to those that are not known to have such an abnormality;
- Clinics must ensure that embryo testing is only carried out for those genetic conditions that are expressly authorised by the Authority;
- It is unlawful to transfer to a woman an embryo that has been subject to a test that supplies genetic information about the embryo unless the test has been expressly authorised by the Authority;
- It is unlawful to use any information derived from tests on an embryo to select embryos of a particular sex for social reasons;
- Clinics may use non-invasive procedures, for example metabolomics, to test and select for the viability of embryos. However, clinics must not use these procedures to test for a specific gene, chromosome, or mitochondrion abnormality without prior authorisation from the Authority.

1.4. The three main types of PGT currently offered to patients in the UK that are established techniques, and already **authorised** for use, therefore will not be covered in this paper, are:

- PGT for monogenetic disease (PGT-M) tests embryos for the presence of a condition caused by a single gene mutation.
- PGT for chromosomal structural rearrangements (PGT-SR) involves looking at the chromosome structure to identify where segments may have been deleted, duplicated, inverted or translocated.
- PGT for aneuploidy (PGT-A) aims to identify embryos carrying an abnormal number of chromosomes, which could lead to miscarriage or IVF failure, and to select euploid (i.e. chromosomally normal) embryos. PGT-A **has been rated 'red'** as a treatment add-on for increasing the chances of having a baby for most fertility patients. This is because PGT-A is a selection tool that often reduces the number of embryos available for transfer.

1.5. PGT for polygenic disorders (PGT-P), also referred to as polygenic risk score (PRS), has become commercially available over recent years. Polygenic disorders are diseases or characteristics where the phenotype of an individual is influenced by multiple genes, for example cancer, heart

disease and diabetes. Embryos are tested and given a 'risk score' of their likelihood of developing a certain disease or characteristic based on their genetic makeup.

1.6. At the June 2024 SCAAC meeting the SCAAC concluded in June 2024 that PGT-P technology is not sufficiently advanced for application in embryo testing, with scores giving information relevant to populations rather than individuals. It was noted that whilst PRS can indicate an increased relative risk to an individual for developing a disease, the absolute risk of developing the disease is likely to be small in most cases. During the June 2024 meeting, the Committee also recommended that the Executive update the patient facing website information on PGT-P. The 'Embryo testing and treatments for disease' webpage has since been updated to clearly state that, in relation to PGT-P, there is currently a lack of evidence to support the use of preimplantation genetic testing for polygenic risk scores and that it is unlawful to do so under the current UK law.

1.7. In February 2026, the HFEA published a blog on PGT-P and an article in the 2 February 2026 edition of BioNews (publication by the Progress Educational Trust [PET]) to clearly explain that PGT-P is unlawful in the UK as it does not fit within any of the permitted purposes under the HFE Act. It specifies that embryos can only be selected for transfer based on information from testing that meets a specified purpose in law. It further explains that the prohibition on performing PGT-P in the UK cannot therefore be circumnavigated by having the analysis carried out in another jurisdiction and then using the results to select embryos.

1.8. At the HFEA's Annual Horizon Scanning Meeting at the European Society for Human Reproduction and Embryology (ESHRE) annual conference in 2024, an invited speaker on the topic of PGT-P highlighted challenges with this method related to reduced number of available embryos, population diversity constraints, and lack of long-term empirical validation for late-onset diseases. Potential harms were also discussed, including unnecessary IVF exposure and discarding viable embryos, variable benefit – harm profiles across patient groups, and shifting reproductive norms. Discussion emphasised that PGT-P is inherently probabilistic, demanding advanced statistical literacy and robust validation thresholds.

1.9. This paper summarises the results of published studies identified within the specified time frame (1st May 2024 to 30th April 2026), during which the literature search was conducted, and it is not an assessment of study validity.

2. Summary of research developments

Sperm selection and testing

Genetic testing of sperm

2.1. Genetic sperm assessment studies analysed differentially expressed genes associated with DNA fragmentation. They identified downregulation of genes linked to oxidative stress and spermatogenesis as well as novel genes involved in DNA fragmentation. Other studies evaluating sperm epigenetic profiles found out men with abnormal sperm epigenetic profiles have lower pregnancy success rates in IUI but not in ICSI. Additional approaches include development of a two-phase deep sequencing assay with unique molecular identifiers for detecting sperm mosaicism, and next-generation sequencing–based karyotyping in men with obstructive and non-obstructive azoospermia undergoing TESE-ICSI.

Microfluidic device – based sperm selection

2.2. Microfluidic sperm selection technologies consistently demonstrate an enhanced capacity to isolate spermatozoa with superior functional and genomic integrity compared with conventional methods such as density gradient centrifugation (DGC), swim-up (SU), and magnetic activated cell sorting (MACS). A key finding across studies is the reduction in sperm DNA fragmentation index (DFI), often accompanied by improvements in progressive motility, morphology, chromatin compaction, mitochondrial membrane potential, and acrosome integrity. Devices based on chemotaxis (induced by microvesicles derived from follicular fluid and cumulus cells), rheotaxis, thermotaxis, or biomimetic reproductive tract models attempt to mimic physiological selection conditions, yielding sperm populations with high motility and intact DNA. While most platforms (eg ZyMot, SwimCount Harvester, LensHooke CA0, and Microfluidic-ICSI-type devices) outperform or match conventional techniques in sperm quality metrics, some variability persists depending on semen characteristics.

2.3. Treatment outcomes are less consistent. Some studies report comparable fertilisation rates and embryo euploidy rates between microfluidic and conventional methods, despite significant reductions in DFI. However, several studies demonstrate higher fertilisation rates and improved embryological outcomes, including higher rates of blastocyst formation and increased proportions of usable and good-quality blastocysts. Improved outcomes appear more pronounced in specific contexts, such as teratozoospermia or elevated baseline DNA damage, where microfluidic selection may better enrich for competent spermatozoa. A recent meta-analysis suggests potential improvements in implantation, clinical pregnancy, and ongoing pregnancy rates, although not uniformly across all endpoints, particularly live birth per first embryo transfer and per concluded cycle.

2.4. Despite two decades of technological and manufacturing advances enabling broader integration of microfluidic devices in assisted reproduction—particularly for sperm selection—clinical adoption remains limited. This is due to scarce long-term outcome data, lack of standardisation across patient populations, and ongoing regulatory challenges (Pensabene *et al.*, 2025).

Artificial Intelligence (AI) – driven sperm selection

2.5. Recent advances in artificial intelligence (AI) and deep learning have aimed at improving sperm assessment, particularly in motility and morphology analysis:

- Novel algorithms incorporating frequency-domain smoothing enable precise extraction of motility parameters and discrimination between hyperactivated and progressive spermatozoa, alongside the introduction of refined kinematic metrics. Computer vision–based models (e.g., Mask R-CNN, YOLO variants, and U-Net) demonstrate differential strengths in segmenting sperm substructures, with performance varying by morphological complexity. A hybrid computer vision–based multi-object tracking approach combining deep learning–driven tracking (BoT-SORT) with probabilistic state estimation using an Extended Kalman Filter (EKF) enables real-time sperm tracking to improve reliability of sperm selection.
- AI-based morphology assessment systems trained on microscopy data improve detection of normal sperm compared to conventional computer-aided analysis. Other AI frameworks for sperm morphology assessment integrate multi-scale part parsing networks that combine semantic and instance segmentation to achieve precise, instance-level

morphological quantification. They also incorporate resolution enhancement techniques to mitigate measurement errors in unstained sperm images. Complementing this, ensemble deep learning approaches leverage CNN-based feature extraction (ie EfficientNetV2) fused with classical machine learning classifiers (SVM, Random Forest, and attention-based MLP) at both feature and decision levels to improve classification accuracy and generalisability. Generative Adversarial Networks (GAN)-driven virtual staining enables real-time, non-invasive visualisation of sperm morphology without the need for chemical staining. An AI model was also developed to classify subcellular structures within sperm cells using features derived from label-free interferometric phase microscopy (IPM), enabling refractive index–based characterization of sperm head components.

- Integrative AI platforms such as Raman-AI assays provide molecular-level, non-invasive sperm profiling by analysing spectral signatures of nucleic acids, proteins, lipids, and glycogen. These features were then linked to fertilisation potential and embryo development outcomes.
- A proof-of-concept study demonstrated automated Day 0 IVF procedures including sperm preparation, cumulus oocyte complex (COC) retrieval, oocyte denudation, and ICSI. It achieved 64.3% fertilisation, 42.2% usable blastocyst formation, and five healthy live births from nine patients (Chavez-Badiola *et al*., 2026).

Other methods for sperm selection and testing

2.6. A range of emerging sperm testing and selection approaches target functional, molecular, and biophysical characteristics beyond conventional morphology and motility assessment. Molecular assays include evaluation of sialylation expression (ie Neuraminidase-1 sialidase), receptor–ligand binding strategies (eg IZUMO1–JUNO interactions), DNA accessibility profiling (NicE-view assay), and analysis of post-translational histone modifications. These studies link sperm quality, fertilisation potential and embryo development.

2.7. Studies evaluating magnetic-activated cell sorting (MACS) show a significant reduction in sperm DNA fragmentation and improved implantation, clinical pregnancy, and live birth rates per embryo transfer in ICSI cycles. This is particularly pronounced in patients with elevated DNA fragmentation, although no benefit is observed in IUI outcomes and comparable results are reported versus TESA for miscarriage and live birth rates.

2.8. Studies on hyaluronic acid–based selection (PICSI), including a prospective triple-blinded RCT in egg donation cycles, report a higher proportion of good-quality day 5 embryos. The same studies also report increased cumulative pregnancy rates compared to conventional ICSI, with other clinical outcomes remaining similar.

2.9. Studies investigating cumulus cell–mediated sperm selection utilise specialised dishes or cumulus cell columns to facilitate sperm–cumulus interaction following DGC. These approaches demonstrate selection of sperm with lower DNA fragmentation, improved embryo developmental kinetics with fewer cleavage abnormalities. In some cases, such approaches find higher pregnancy and live birth rates, while others report no differences in blastocyst formation or pregnancy rates.

2.10. Advanced imaging for non-invasive sperm selection using quantitative phase microscopy (QPM) enables high-resolution, label-free 3D morphological analysis, demonstrating improved pregnancy and live birth outcomes compared to conventional ICSI and IMSI.

2.11. Additionally, selection techniques such as zeta potential, birefringence, and free centrifuge sorting (FCS) aim to enrich for sperm with improved DNA integrity and overall quality.

Reviews

2.12. Several reviews summarise emerging sperm selection and assessment strategies, including sperm gene sequencing microfluidics, MACS, artificial intelligence, Raman spectroscopy, advanced imaging (eg 3D and high-precision microscopy), and analysis of seminal plasma exosomes. They highlight ongoing challenges in clinical translation, emphasising the need for large-scale validation and long-term safety data.

Oocyte selection and testing

2.13. Studies on non-invasive oocyte quality assessment use multi-omics analyses of follicular fluid (FF), cumulus cells, and granulosa cells (GCs) to identify molecular signatures linked to oocyte competence. Transcriptomic and metabolomic profiling of FF from PCOS patients reveals dysregulation of pathways such as citrate cycle, oxidative phosphorylation, mTOR, and steroid biosynthesis, with specific metabolites (eg L-arginine, estrone sulphate) correlating negatively with fertilisation and embryo quality.

2.14. MicroRNA (miRNA) profiling in FF shows associations between elevated plasma bilirubin and miRNA signatures that target key inflammatory mediators, with higher miRNA transcript levels linked to lower fertilisation rates. Proteomic analysis identifies proteins such as immunoglobulin heavy constant alpha 1 (IgA1hc) and dickkopf-related protein 3 that differ between oocytes leading to poor versus high-quality embryos.

2.15. Metabolomic profiling of GCs demonstrates that mitochondrial respiration and glycolysis associated with fertilisation outcomes and embryo development. Fluorescence lifetime imaging microscopy (FLIM)-based metabolic imaging of cumulus cells reveals FAD+ parameters correlated with blastocyst quality, clinical pregnancy, and live birth outcomes.

Reviews

2.16. Reviews summarise emerging determinants of oocyte quality, including the oocyte cortex and its mechanical properties as potential non-invasive biomarkers of developmental competence. They also explore ferroptosis within the follicular environment, linking oxidative stress and lipid peroxidation to impaired oocyte maturation and fertility outcomes. Additionally, follicular fluid is highlighted as a source of multi-omics biomarkers.

Embryo testing

Non-invasive methods for ploidy analysis

2.17. Many studies investigate the use of cell-free DNA (cfDNA) from spent culture media (SCM) or blastocoel fluid as a non-invasive alternative (niPGT-A) to trophectoderm (TE) biopsy, with generally variable concordance between methods. While informativity can be high – particularly with optimised workflows such as double amplification, assisted hatching, or extended culture to

day 6 – diagnostic performance remains inconsistent, with moderate concordance rates and variable sensitivity and specificity for aneuploidy detection across studies and centres. A recurring limitation is maternal DNA contamination, alongside technical variability, which impacts accuracy and interpretability.

2.18. Several studies highlight clinically relevant discordance, particularly false-positive aneuploid classifications by niPGT-A, where embryos deemed aneuploid still resulted in successful pregnancies and live births, raising concerns about potential exclusion of viable embryos. However, protocol modifications required to implement niPGT-A do not appear to adversely affect blastocyst yield or pregnancy outcomes. Emerging approaches, including biosensor-based mutation detection and optimised analytical pipelines, may improve predictive performance, although other biomarkers such as mitochondrial DNA copy number in SCM demonstrate limited clinical utility.

2.19. In conventional PGT-A cycles, studies evaluating embryo morphokinetics demonstrate that chromosomal abnormalities such as deletions, duplications, and monosomies are associated with delayed morphokinetic progression. This arises particularly during cleavage and blastocyst stages, with notable effects for chromosomes 20 and 22. Morphology-based assessments in PGT-A cycles show that embryo morphology is associated with genetic status, and higher-quality inner cell mass (ICM) and trophectoderm (TE) grades are linked to increased euploidy rates. In older patients (>35 years), non-invasive chromosome screening (NICS) yielded outcomes comparable to conventional PGT-A, showing improved cumulative live birth rates and reduced pregnancy loss compared to ICSI only cycles.

2.20. AI-based embryo assessment in PGT cycles demonstrates that higher iDAScore values were associated with euploidy, with predictive performance further improved by incorporating clinical and embryonic variables. More broadly, ensemble AI models integrating embryo and maternal features outperform experienced embryologists in predicting embryo selection outcomes including aneuploidy.

Non-invasive methods for analysis of other embryo parameters

2.21. The Alpha Scientists in Reproductive Medicine/ESHRE consensus on oocyte and embryo morphological assessment from 2011 was updated and published in Human Reproduction journal (The Working Group on the update of the ESHRE/ALPHA Istanbul Consensus, 2025).

2.22. Studies on non-invasive embryo assessment identify miRNAs in blastocoel fluid as biomarkers of blastocyst quality and implantation potential. These studies show upregulation of miRNAs in implanted embryos related to pluripotency- and cell growth-related pathways. Additional approaches were developed to predict embryo implantation potential and to improve clinical outcomes. They assess cytokines or multi-protein profiles in SCM, as well as cumulus cell metabolic signatures via FLIM.

2.23. Imaging-based methods incorporate time-lapse parameters, multi-focal image fusion, and 3D reconstruction to enhance morphological assessment. Findings show that fragmentation and blastocyst collapse are associated with reduced embryo quality and lower chromosomal normalcy. Novel metrics such as densification index of the ICM were shown to be associated with euploidy and better pregnancy and life birth rates. Modified grading systems for borderline

blastocysts highlight reduced clinical pregnancy and live birth rates in embryos with lower quality ICM.

Metabolomic profiling

2.24. Studies investigate non-invasive embryo assessment using SCM metabolomics, linking the time-lapse imaging morphokinetic parameter S2 to distinct metabolic pathway activity and moderate predictive capacity for embryo development. Other data identify specific metabolites, including benzoic acid, associated with implantation outcomes in cleavage-stage embryos. Multi-omics (proteomic and metabolomic) profiling of morphologically high-quality embryos further reveals molecular signatures correlated with clinical implantation success. Across discovery and validation cohorts using embryos with known implantation potential (PGT-A and non-PGT-A cycles), metabolite concentrations consistently correlate with implantation outcomes, and AI-based integration of these biomarkers improves predictive power.

Invasive embryo testing

2.25. Studies describe integrated PGT approaches combining PGT-A, PGT-M, and PGT-SR using low-pass whole-genome sequencing, Multiple Annealing and Looping-Based Amplification Cycles (MALBAC), and link-read sequencing for comprehensive embryo genetic analysis. They show high concordance to standard methods:

- Phbol-seq uses link-read sequencing with an error-correction algorithm to distinguish assembly errors from homologous recombination. It enabled accurate haplotyping with >95% concordance and full embryo-level diagnostic agreement.
- KaryoSeq integrates low-coverage whole-genome sequencing with depth optimisation, achieving 100% concordance. It detected additional abnormalities including triploidy, uniparental disomy, and maternal contamination.

2.26. Single-case studies show that chromosome conformation based Karyotyping technique (C-MoKA) can identify complex chromosomal rearrangements and breakpoints to distinguish carrier from normal embryos. Other approaches combine high-resolution PGT-A/PGT-M to detect small fragment copy number variation (CNVs) and prevent transmission of disorders such as Charcot-Marie-Tooth disease type 1A. Another study show that PGT combining low-coverage next-generation sequencing and SNP linkage analysis can block transmission of deafness-related mutations.

Reviews

2.27. Reviews highlight multiple non-invasive approaches for embryo assessment, including cfDNA-based ploidy testing from spent culture media and blastocoel fluid, and AI-driven embryo ploidy inference. Other approaches include metabolomics, extracellular vesicle (EV) analysis of miRNAs and transcription factors, secretome profiling of cfDNA, mitochondrial DNA (mtDNA) and small non-coding RNAs. These techniques aim to evaluate embryo viability, genetic integrity, and implantation potential, with AI supporting decision-making and molecular biomarkers (e.g., miRNAs, cfDNA, mtDNA) reflecting developmental competence.

2.28. For cfDNA-based ploidy testing, key challenges include maternal/exogenous DNA contamination, DNA amplification failure, diagnostic inaccuracies, and only moderate concordance with TE biopsy, particularly for mosaicism and segmental aneuploidies. In contrast, other approaches

such as EVs, secretome analysis, and metabolomics face issues related to lack of standardisation, undisclosed culture media composition, and predominantly qualitative outputs, limiting reproducibility and clinical translation.

PGT for polygenic disorders (PGT-P) embryo screening

2.29. Several reviews consistently characterise PGT-P as a promising but insufficiently validated technology with uncertain predictive power, limited evidence of clinical utility, and unclear long-term outcomes. Across the literature, major concerns include socio-ethical risks (eg stigma, false expectations, inequity), substantial counselling and implementation burdens, and challenges in establishing accuracy, clinical validation and representativeness. These studies further emphasise the need for robust ethical, clinical, and regulatory guidelines before clinical adoption. They also draw particular focus on reproductive autonomy, appropriate target populations, and the boundary between disease prevention and enhancement.

2.30. Several opinion articles on PGT-P explore its ethical, regulatory, and sociocultural dimensions, highlighting cross-national differences in governance (eg, USA, Israel, Germany). These differences include proposed safeguards to restrict its use to clinically relevant polygenic disease traits prevention, and the importance of rigorous genetic counselling and controlled access to raw genetic data. They also examine sociocultural drivers of acceptance – such as greater openness to cognitive enhancement in East Asian context – and identify emerging challenges including decision fatigue, choice overload, and legal concerns around informed consent and truthful marketing.

2.31. An opinion piece critiques the use of UK Biobank data, arguing that some downstream applications – such as developing polygenic scores for traits like intelligence for commercial embryo screening – may fall outside the scope of participant consent. This raises concerns about inadequate safeguards, dual-use risks, and misalignment with the project's stated public-interest aims (Barn, 2025).

2.32. A statement by the American College of Medical Genetics and Genomics (ACMG) evaluates the clinical application of PGT-P within IVF, highlighting methodological and translational challenges in applying adult-derived polygenic risk scores to embryo selection. They have concluded that current evidence does not demonstrate clear clinical utility (Grebe *et al*., 2024).

2.33. The Ethics Committee of the American Society for Reproductive Medicine and the Practice Committee of the American Society for Reproductive Medicine have issued an opinion addressing the ethical implications of PGT-P in reproductive medicine (Ethics Committee and Practice Committee of ASRM, 2026).

3. Recommendations

3.1. Members are asked to:

- Consider the progress of research into embryo and gamete testing;
- Advise the Executive if they are aware of any other recent developments;
- Review whether any outputs from the HFEA are required addressing the use of emerging technologies in embryo and gamete testing.

4. References

Barn G. Consent and its discontents: the case of UK Biobank. *Med Health Care Philos*. 2025 Sep; 28(3):533-547.

Chavez-Badiola A, Mendizabal-Ruiz G, Flores-Saiffe Farías A, Costa-Borges N, Murray A, Alikani M, Silvestri G, Millan C, Hernández-Morales E, Valencia-Murillo R, Medina V, Mestres E, Valadez Aguilar A, Ocegueda-Hernández V, Acosta-Gómez F, Álvarez López A, Acacio M, Matia-Algué Q, Espinoza Figueroa JG, Campos Olmedo LM, Barragan CP, Sánchez-González DJ, Cohen J. Automated oocyte retrieval, denudation, sperm preparation, and ICSI in the IVF laboratory: a proof-of-concept study and report of the first live births. *Hum Reprod*. 2026 Feb; 41(2): 214–230.

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Grebe TA, Khushf G, Greally JM, Turley P, Foyouzi N, Rabin-Havt S, Berkman BE, Pope K, Vatta M, Kaur S; ACMG Social, Ethical, and Legal Issues Committee. Clinical utility of polygenic risk scores for embryo selection: A points to consider statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2024 Apr; 26(4):101052.

Pensabene V, Agate F, Santos Miranda A, Picton HP. Microfluidics for *in vitro* fertilization: from science to clinical validation. *Hum Reprod Update*. 2025 Dec; 32(2):206–230.

5. Annex A – Literature review and scope of Emerging technologies in embryo and gamete testing

5.1. Annex A has been circulated to the committee as a separate Excel document, which provides details on the available research on Emerging technologies in embryo and gamete testing published between 1st May 2024 and 30th April 2026.

5.2. This topic includes research advancements in gamete and embryo testing methods, including but not limited to:

- non-invasive embryo testing for PGT-M and PGT-A
- advances in whole genome and exome sequencing and novel PGT methods (eg mitochondrial copy number, segmental aneuploidy, PGT-P, etc)
- metabolomic profiling and other parameters indicating embryo health and quality
- morphological grading with biopsy, novel blastocyst scoring systems, analysis of follicular fluid and cumulus cells

- emerging and novel oocyte and sperm testing and selection methods.
- genetic testing of sperm is considered within scope

5.3. Studies on sperm DNA fragmentation testing and resulting management or outcomes is now excluded from the search as it is considered under the treatment add-on 'Sperm DNA fragmentation testing'. The topics excludes literature search on AI in fertility treatment, which is a separate horizon scanning topic, but includes literature on the use of AI as a non-invasive tool for ploidy inference of the embryo.

5.4. At the February 2025 SCAAC meeting, the Executive **introduced** a list of 'watching brief' topics to help the SCAAC monitor issues that present concerns or opportunities which may warrant continued oversight by the Committee. In light that the topic of 'Understanding the genetic basis of infertility' was added to this list, the Executive **proposed** that genetic testing (through blood) for male infertility will be removed from the scope of the 'Emerging technologies in gamete and embryo testing' topic.

5.5. The topic search strategy, originally developed in PubMed, was adapted for Ovid Medline to align with the methodology developed for the treatment add-ons literature search, and to ensure comprehensive coverage across platforms.

Impact of the microbiome on fertility and fertility treatment outcomes

Details about this paper

Area(s) of strategy this paper relates to:	Supporting scientific and medical innovation
Meeting:	Scientific and Clinical Advances Advisory Committee (SCAAC)
Agenda item:	6
Paper number:	HFEA (03/06/2026) 006
Meeting date:	03 June 2026
Author:	Dharmi Deugi, Scientific Policy Officer (HFEA)
Annexes	Annex B – Literature review and scope of the Impact of the microbiome on fertility and fertility treatment outcomes

Output from this paper

For information or recommendation?	For recommendation
Recommendation:	Members are asked to: • advise the executive if they are aware of any other recent developments; • consider the research findings, drawing conclusions on what influence the microbiome may have on fertility and fertility treatment outcomes; and • review whether any outputs from the HFEA are required.
Resource implications:	Within budget
Implementation date:	N/A
Communication(s):	Minutes of committee discussion to be published on the SCAAC webpage and communicated to the sector via Clinic Focus newsletter.
Organisational risk:	Low

1. Background

1.1. The microbiome refers to the community of microorganisms – primarily bacteria, but also fungi and viruses – that inhabit various parts of the human body, including the gut, skin, and reproductive tract. Research in this area investigates how the microbiome may influence reproductive health and outcomes, for example through imbalances in microbiome composition. If the composition of the microbiome is shown to be related to fertility or fertility treatment outcomes, understanding this relationship will have implications for managing infertility with the potential for development of interventions to improve outcomes for patients.

1.2. The 'Impact of the microbiome on fertility and fertility treatment outcomes' topic was introduced to the SCAAC's horizon scanning prioritised list in **February 2018** and last discussed at the **June 2025** SCAAC meeting.

1.3. In **June 2025**, the Committee highlighted concerns about the clinical use and communication of microbiome testing in fertility treatment. Members noted that microbiome tests provide only a time-point "snapshot" that may not reflect microbial composition at point of treatment and noted that both partners may need testing. The increasing promotion of testing and related products through private providers and social media was also considered problematic, as patients may struggle to distinguish marketing from evidence-based advice.

1.4. Members also flagged the limited evidence supporting interventions such as, prebiotics, probiotics and antibiotics, highlighting risks of potential antimicrobial resistance and use of unregulated products. Overall, the Committee concluded that evidence for microbiome testing and related interventions remains limited and methodologically constrained, with only preliminary evidence linking Lactobacillus dominance to improved reproductive outcomes.

1.5. In **February 2026**, the Committee noted a study led by the **Medicines and Healthcare products Regulatory Agency (MHRA)** which revealed significant variability in microbiome research methods across the world. The study established Minimum Quality Criteria for four key reporting measures that laboratories worldwide can now use to validate their microbiome analysis methods.

1.6. This paper presents literature published between 2nd May 2025 and 29th April 2026 investigating the possible relationship between the microbiome and fertility or fertility treatment outcomes. The literature search across this date range identified relatively few studies on interventions and therapeutic strategies for the microbiome. This is consistent with the results from the **previous literature search** conducted on this topic between September 2023 and May 2025. The Executive notes that this paper provides a summary of the findings described in published literature and is not an assessment of study validity.

2. Summary of research developments

2.1. Since this topic was last reviewed in **June 2025**, a growing body of research has emphasised the complex, multi-factorial nature of the relationship between microbial composition in the female reproductive tract and reproductive success.

2.2. The evidence consistently finds that a Lactobacillus-dominated reproductive tract microbiome is associated with improved ART outcomes. However, reproductive success appears to depend not only on Lactobacillus presence but also on species composition (e.g., L. crispatus vs L. iners), microbial stability, and their functional activity. Increased microbial diversity of non-Lactobacillus taxa may be linked to less favourable outcomes, potentially mediated through inflammatory pathways and microbial metabolites which impair endometrial barrier function. Furthermore, vaginal and endometrial microbiomes represent distinct but complementary niches, both contributing to ART outcomes.

2.3. Distinct microbial and metabolic signatures are reported across conditions such as PCOS, adenomyosis, endometriosis, chronic endometritis, and pelvic inflammatory disease, although findings remain limited and contradictory. Notably, emerging research highlights the importance of non-bacterial components, such as the gut mycobiome, and cross-kingdom microbial interactions in disease pathogenesis.

2.4. Fertility outcomes may also be shaped by hormonal, environmental and disease-related factors. Additionally, host-microbe interactions, such as, immune modulation and metabolite production can also play a role. Mechanistic studies demonstrate that dysbiosis can disrupt immune tolerance, promote inflammation, and alter endometrial receptivity through pathways such as microbial metabolite signalling and cell regulation. Research indicates that species-specific effects and microbial functional traits may be critical determinants of fertility outcomes.

2.5. Emerging evidence extends the role of the microbiome in reproductive health beyond the reproductive tract, highlighting the oral and gut microbiomes as potential important systemic regulators of reproductive success. Imbalances across these niches could be linked to adverse outcomes, with the gut microbiome in particular playing a central role in the gut–reproductive axis, where it may influence fertility through immune, metabolic, and endocrine mechanisms.

2.6. Microbiome research has consistently expanded to consider the role of the male reproductive tract, where seminal microbial species may influence sperm quality and fertility, indicating that both partners microbiomes may play a role in reproductive success. Novel research suggests partner microbiome interactions and microbial exchange may contribute to outcomes, though data remains limited and largely associative.

2.7. The evidence base on the microbiome in infertility remains largely experimental, with limited consensus on clinically relevant microbial profiles and inconclusive support for routine diagnostic testing or targeted interventions. Although some studies report benefits in shifting microbiota toward Lactobacillus dominance through interventions, such as probiotics and microbial transfer, others highlight inconsistent efficacy and potential risks, including disruption of beneficial microbiota. Reports on consistent improvements in fertility outcomes are limited, and causal relationships remain unclear.

2.8. Overall, evidence suggesting that fertility could be influenced by interactions between microbiomes across multiple sites, including the reproductive tract and gut, alongside host-related factors, such as metabolic, immune and hormonal, remains limited. Significant heterogeneity highlights the need for standardised, longitudinal, and mechanistic studies to enable clinical translation.

3. Recommendations

3.1. Members are asked to:

- Advise the executive if they are aware of any other recent developments;
- Consider the research findings, drawing conclusions on what influence the microbiome may have on fertility and fertility treatment outcomes; and
- Review whether any outputs from the HFEA are required.

4. Annex B – Literature review and scope of Impact of the microbiome on fertility and fertility treatment outcomes

4.1. Annex B has been circulated to the committee as a separate Excel document, which provides details on the available research on the impact of the microbiome on fertility and fertility treatment outcomes published between 2nd May 2025 and 29th April 2026. Where possible literature has been separated by relevant subheadings.

4.2. This topic includes research advancements on the microbiome with relevance to fertility treatment in the following areas: (1) understanding the normative microbiota composition of the reproductive tract, (2) understanding an association between reproductive tract microbiota and its role in fertility/infertility, (3) developing interventions to improve fertility and fertility treatment outcomes.

4.3. The topic search strategy, originally developed in PubMed, was adapted for Ovid Medline to align with the methodology developed for the treatment add-ons literature search, and to ensure comprehensive coverage across platforms.

Rating review for treatment add-on – Microbiome testing

Details about this paper

Area(s) of strategy this paper relates to:	Regulating a changing environment
Meeting:	Scientific and Clinical Advances Advisory Committee (SCAAC)
Agenda item:	7
Paper number:	HFEA (03/06/2026) 007
Meeting date:	3 June 2026
Authors:	Rebecca Taylor, Scientific Policy Manager
Annexes	Annex A: Evidence decision tree for rating add-ons Annex B: References - studies considered but not included in rating review Annex C: Expert statistician's independent report

Output from this paper

For information or recommendation?	For recommendation
Recommendation:	Members are asked to: • consider the quality of evidence for the use of microbiome testing and arising recommendations as a treatment add-on based on the findings from an independent assessor; • agree and recommend ratings for each outcome(s) and population(s); • consider how the ratings might be presented to the public on the HFEA website.
Resource implications:	In budget
Implementation date:	Recommendations will be implemented as soon as feasible
Communication(s):	Updates to the HFEA's website information on treatment add-ons and communication of updates to the sector, patients and public.
Organisational risk:	Low

1. Background

1.1. Treatment add-ons are often non-essential treatments or tests that may be offered in fertility clinics in addition to routine treatment with the claim that they can improve treatment outcomes.

1.2. Tests were added to the add-on definition in July 2025, following a proposal from the SCAAC which was agreed by the Authority.

1.3. In relation to tests, it is not expected that the HFEA would undertake a review on the accuracy of the testing, but the impact on fertility treatment outcomes of recommended action arising from test results.

1.4. As with all new treatments, tests or technologies being introduced into reproductive medicine, the HFEA expect the introduction of treatment add-ons into clinics to be preceded by good quality scientific research into the effectiveness and safety of these interventions. However, some treatment add-ons are being offered to patients despite a lack of evidence for effectiveness at increasing live birth rate, improving safety, or other treatment outcomes such as reducing the chance of miscarriage. They are frequently offered outside of a research setting and are subject to additional costs for the patient.

1.5. HFEA and eight professional and patient bodies have committed to monitor the evidence base for treatment add-ons and their offering in UK clinics in a **consensus statement**.

1.6. Medical professionals, academics or patient organisations can propose that we review the evidence base for a treatment or test add-on if they are concerned that it is being offered to patients in a UK licensed clinic:

- with the claim that it will increase the live birth rate or improve other treatment outcomes;
- without conclusive evidence of its effectiveness at improving the live birth rate or other treatment outcomes;
- it is not already listed in our the HFEA's rated list of add-ons; or
- there is evidence that an add-on treatment or test may reduce treatment effectiveness or there are potential safety concerns.

1.7. Microbiome testing as an add-on arose in discussions of a literature review on microbiome at the **June 2025 SCAAC meeting**. SCAAC members noted the increased commercialisation of microbiome testing targeted at fertility patients as well as advice or recommended interventions arising from test results such as probiotics. Members recommended that, subject to a small change in the definition of add-on being approved by the Authority, microbiome testing should be rated as an add-on.

1.8. At the July 2025 Authority meeting, it was agreed to change the definition of a treatment add-on to include tests. (See **meeting minutes**, page 3).

1.9. An add-on review panel took place on 10 November 2025. The panel agreed that:

- The populations of interest were:
  - Female – general fertility patient population
  - Female – recurrent implantation failure (RIF)
  - Female – repeated pregnancy loss (RPL)
  - Male – general fertility patient population (idiopathic infertility/male factor infertility)

- The outcomes of interest were:
  - Live birth
  - (if live birth not available) ongoing pregnancy rate and/or clinical pregnancy rate
  - Miscarriage rate

The panel also noted the following:

- Male factor infertility is likely to include those with anti-sperm antibodies and recurrent pyospermia.
- Add-ons review will not target specific microbiome interventions, but they are likely to come out in the literature review. It will then be necessary to group the studies e.g. all studies using probiotics, all studies using antibiotics etc.
- In relation to the commercial tests available such as EMMA and ALICE, if one type of test showed changes in outcomes of interest, it would be appropriate to note this.

2. Literature search – updated process

2.1. The MEDLINE (Ovid) database, along with two clinical trial registries in line with Cochrane (International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov) were used to carry out the literature search[1].

2.2. The literature search first identified relevant randomised controlled trials (RCTs) and systematic reviews. This identified:

- Two RCTs looking at the use of probiotics in patients with recurrent implantation failure (RIF)
- Two RCTs looking at the use of probiotics in female fertility patients
- One RCT treating female fertility patients with intestinal dysbiosis probiotics combined with prebiotics
- One RCT treating female fertility patients with abnormal microbiota with probiotics combined with antibiotics
- One RCT treating female fertility patients with antibiotics

2.3. Given the low number of RCTs identified for the target patient populations and interventions, the search was expanded to non-randomised studies of intervention (NRSIs) which are limited to case/cohort/control studies. Fifteen studies were found:

- Four studies on probiotic treatment in female fertility patients, including one on patients found to have dysbiosis.
- One study on probiotic treatment in patients with recurrent pregnancy loss (RPL)
- Two studies on combined antibiotic and probiotic treatment, one for dysbiosis/ultra-low biomass, the other for repeated implantation failure (RIF)
- Two studies on antibiotic treatment for general female fertility patients.
- One study on antibiotics in patients with RIF.

[1] In line with the decision tree found at Annex A, neither pre-prints nor abstracts are included in the evidence base.

- One study on antibiotic or combined antibiotic and probiotic treatment for patients with chronic endometritis (CE).
- Four studies on antibiotic treatment for patients with CE.

2.4. At the February 2017 SCAAC meeting, it was agreed that evidence published in the last 10 years would be sent for review. The literature search covered the period of February 2016 to February 2026. However, the studies found date from 2017 to 2025.

3. Independent assessment of the quality of evidence

3.1. In order to categorise the treatment add-ons under consideration, it is necessary not only to identify the published evidence on each treatment add-on, but also to assess the quality of that evidence. For this reason, we seek advice from an expert in systematic reviews and evidence assessment to carry out an independent assessment of the quality of evidence (using the GRADE methodology[2]) for each treatment add-on.

3.2. The critical review of studies included assessment of risk of bias from allocation method, blinding, selective reporting, unexplained attrition, unplanned interim analysis and other miscellaneous errors in the design, conduct or reporting of results. However, the assessments made by the independent reviewer are from a methodological perspective without expertise in the clinical or scientific context.

3.3. Findings of the independent assessment for microbiome testing can be found in Annex C, the report of the external expert statistician. This report details the independent reviewers recommended rating in relation to the HFEA's five-category rating system, along with the studies used in the assessment. Other studies that were considered, but not used in the assessment are listed in Annex B.

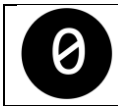
4. The five-category rating system

4.1. The decision tree for determining how evidence will be used by SCAAC when assigning add-ons rating can be found at Annex A.

4.2. The Authority approved a five-category rating system with the following symbols/colours and definitions in July 2022:

	On balance, findings from high quality evidence shows this add-on **is effective at improving the treatment outcome**.
	On balance, it is **not clear whether this add-on is effective at improving the treatment outcome**. This is because there is conflicting moderate/high quality evidence – in some studies the add-on has been found to be effective, but in other studies it has not.
	**We cannot rate the effectiveness of this add-on at improving the treatment outcome** as there is insufficient moderate/high quality evidence.

[2] GRADE is an approach for grading the quality of evidence and the strength of recommendations. It was developed by the Grading of Recommendations, Assessment, Development and Evaluation Working Group.

	On balance, the findings from moderate/high quality evidence shows that **this add-on has no effect on the treatment outcome**.
	There are **potential safety concerns and/or**, on balance, the findings from moderate/high quality evidence shows that **this add-on may reduce treatment effectiveness**.

4.3. Most treatment add-ons on our website will have a rating to indicate whether the evidence shows that the treatment add-on is effective at improving the chances of having a baby for most fertility patients. However, as approved by the Authority, the five-category rating system may also be applied to additional outcomes, such as miscarriage, and outcomes for specific patient groups, such as those diagnosed with male-factor infertility.

5. Considerations and recommendations for rating microbiome testing and interventions arising from testing

5.1. A literature review on the impact of the microbiome on fertility and fertility treatment outcomes is also being presented at the June 2026 SCAAC meeting.

5.2. The 2026 NICE guideline on Fertility problems: assessment and treatment (NG 257) does not recommend microbiome testing. This is encapsulated within a recommendation on endometrial receptivity testing, which is as follows:

- 1.41.1: “Do not offer endometrial receptivity testing as a treatment add-on for embryo transfer. This includes both gene expression analysis (for example, endometrial receptivity array) and microbiological analysis (for example, endometrial microbiome metagenomic analysis, analysis of infectious chronic endometritis).”

- The reasoning behind the recommendation was that “There was no evidence on treatment of endometrial abnormalities related to the microbiome or microbiological analysis, so the committee made a recommendation for research on treatments based on endometrial receptivity testing.”

5.3. The NICE guideline recommendation on research as mentioned above notes that the following research question needs addressing:

- Do treatments for identified endometrial abnormalities related to the microbiome or microbiological analysis (such as antibiotics to treat endometritis or microbiota transplantation) improve reproductive outcomes for people undergoing assisted reproduction?

5.4. The European Society of Human Reproduction and Embryology (ESHRE)’s latest good practice recommendations on add-ons in reproductive medicine did not consider microbiome testing or treatments (Lundin et al., 2023).

5.5. The European Association of Urology Guidelines on Male Sexual and Reproductive Health (Minhas et al., 2025) do address the use of probiotic treatment, which is an intervention that can be recommended based on microbiome testing results. The guidelines make no recommendation on the use of probiotics or prebiotics and conclude that “Further

high-powered RCTs are warranted to further investigate the use of prebiotic/probiotic supplementation in the context of male infertility".

5.6. There are a variety of different tests used to assess microbiome in fertility patients. These include:

- EMMA (Endometria Microbiome Metagenomic Analysis) test, which assesses the endometrial microbial environment and is usually offered alongside ALICE (Analysis of Infectious Chronic Endometritis) test. (**Further information about EMMA and ALICE from manufacturer**).
- Next generation sequencing (165 rRNA sequencing or shotgun metagenomics) to assess microbiome for fertility. Examples of such tests include:
- **ScreenMe** which is offered for male (**semen** microbiome) and female (**vaginal** and **uterine** microbiome) fertility patients. It promises to screen for all lactobacilli, all commensal and pathogenic bacteria and all yeast and fungi.
- **Fertylisis vaginal microbiome**
- **MicroGenDx WomensKey** and **MicroGenDx MensKey.**
- Medicover Genetics which offers **Ebiom+** for "comprehensive endometrial microbiome analysis to support fertility care" using NGS and PCR technology as well as ebiomCE, a PCR test to identify STDs and diagnose chronic endometritis.
- PCR testing, such as that offered by **YourDaye**, which screens for Lactobacilli, common BV related bacteria, Candida, Mycoplasma hominis, Mycoplasma genitalium and Ureaplasma.
- Endometrial microbiome testing from **BioBloomLife**.

5.7. Fertility clinics market microbiome testing in a number of ways including:

- For unexplained fertility, repeated implantation failure or endometriosis, for example **Care Fertility propose EMMA and ALICE** for these reasons.
- As part of a group of tests to assess endometrial health in female fertility patients. For example **CRGH** proposes EMMA and ALICE alongside ERA and NK tests.
- Harley Street Fertility Clinic **propose EMMA.**
- North West Fertility **Emma and Alice – North West Fertility**
- The **Hewitt Fertility Centre** propose EMMA and ALICE alongside ERA testing.
- **Fertility Solutions** offer male and female microbiome testing, marketing vaginal microbiome testing as a possible "missing piece" for patients failing to conceive, miscarrying or experiencing failed IVF.

5.8. There are also some companies which offer direct-to-consumer microbiome testing for fertility such as **Juno Bio** who offer direct-to-consumer vaginal microbiome testing using NGS technology.

5.9. It is also possible to find health and wellness clinics (which are not registered fertility clinics) that offer microbiome testing. For example, **The Fertility Suite**, which has six clinics in different parts of the UK offers fertility consultations that may advise vaginal microbiome testing (using ScreenMe).

Expert review April 2026

GREY for live birth for general female fertility patient population.

Interventions following microbiome testing comprised:

- probiotics
- probiotics with antibiotics
- antibiotics

It is uncertain whether the interventions improved live birth as the quality of the evidence in published studies was considered low or very low.

GREY for clinical pregnancy or ongoing pregnancy rate and miscarriage for general female fertility patient population.

Interventions following microbiome testing as under live birth above.

It is uncertain whether the interventions improved treatment outcomes as the quality of the evidence in published studies was considered low or very low.

GREY for live birth for patients with repeated implantation failure (RIF)

Interventions following microbiome testing for patients with RIF were:

- probiotics
- probiotics with antibiotics
- antibiotics

It is uncertain whether the interventions improved live birth as the quality of the evidence in published studies was considered low or very low.

GREY for clinical pregnancy rate, ongoing pregnancy rate and miscarriage for patients with repeated implantation failure (RIF). There were no studies addressing miscarriage in patients with RIF.

Interventions following microbiome testing as under live birth above.

It is uncertain whether the interventions improved ongoing pregnancy rate as the quality of the evidence in published studies was considered low or very low. While several studies suggested probiotics and antibiotics may improve clinical pregnancy, the quality of the evidence was considered low.

GREY for live birth for patients identified as having abnormal vaginal microbiota/intestinal dysbiosis

Interventions following microbiome testing were:

- probiotics
- probiotics with antibiotics
- antibiotics

While one study suggested antibiotics may improve live birth in women with intestinal dysbiosis, the quality of the evidence was considered very low.

GREY for clinical and ongoing pregnancy rate for patients identified as having abnormal vaginal microbiota/intestinal dysbiosis

Interventions following microbiome testing were:

- probiotics
- probiotics with antibiotics
- antibiotics

The quality of the evidence in published studies was considered very low.

GREY for live birth for patients diagnosed with chronic endometritis.

Interventions following microbiome testing were:

- antibiotics
- antibiotics with probiotics

The published studies showed no clear difference in live birth and quality of the evidence in was considered very low.

GREY for clinical pregnancy rate, ongoing pregnancy rate and miscarriage for patients diagnosed with chronic endometritis

Interventions following microbiome testing as above.
The published studies found no clear difference for miscarriage, clinical pregnancy or ongoing pregnancy, and the quality of the evidence in was considered low.

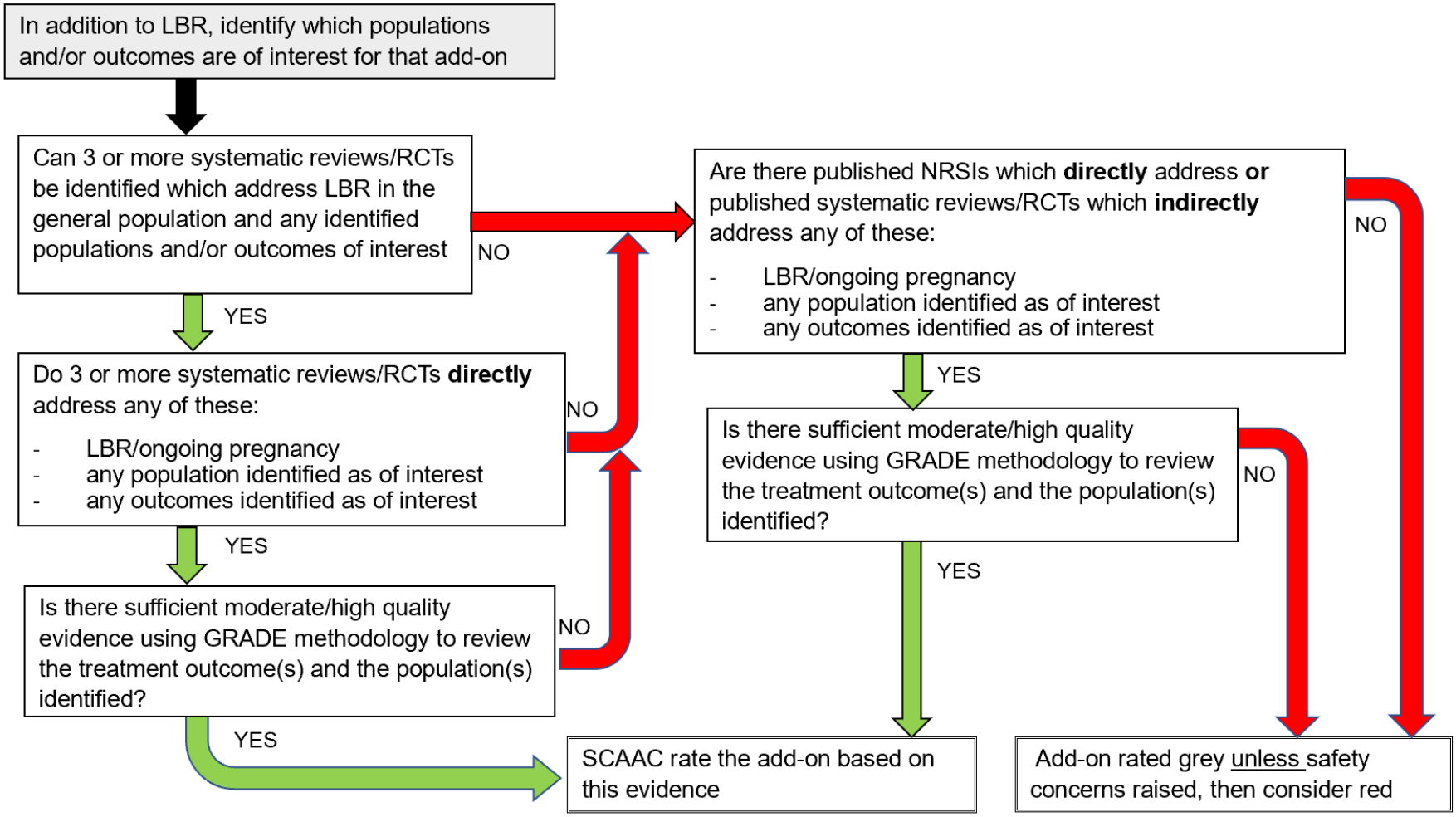
6. Recommendations

6.1.

Members are asked to:

- consider the quality of evidence for microbiome testing as a treatment add-on based on the findings from an independent assessor; and
- agree and recommend ratings for each outcome(s) and population(s)
- consider how the ratings might be presented to the public on the HFEA website, for example the level of detail on interventions and sub-groups arising from the studies

7. Annex A: Evidence decision tree for rating add-on



8. Annex B: References - studies considered but not included in rating review

The studies used in the rating review are listed in the expert report (Annex C). Some other studies were provided for consideration but were not used in the rating review. They were as follows:

- Ameratunga et al (2021), **https://doi.org/10.1002%2F14651858.CD008995.pub3** – Updated Cochrane systematic review of two studies, one of which is included in the analysis (Eskew, 2021) and the other is from 2005, so falls outside the time frame.
- Corbett et al (2021), **https://doi.org/10.1016/j.ejogrb.2020.10.054** – Systematic review of four studies. Two of the studies in the review did not meet the add-on inclusion criteria as they did not address ART outcomes. One study was outside the timeframe (2005), and the remaining study was excluded as it did not fully report target outcomes.
- Fernandez et al (2021), **https://doi.org/10.3390/nu13010162** - study excluded as it looks at couples conceiving naturally.
- Inestia et al, (2022), **https://www.mdpi.com/2076-2607/11/11/2796** - excluded as study does not contain a control group.
- Maleki-Hajiagha et al (2025), **https://doi.org/10.1186/s12884-025-07338-0**– Systematic review and meta-analysis of six studies, four of which are included in the analysis. Of the remaining studies, one fell outside the time frame (2005) and the other was published only in Chinese.
- Santana Almeida et al (2024), **https://doi.org/10.61622/rbgo/2024rbgo82** - Systematic review of six studies, four of which are included in the analysis. Of the remaining studies, one falls outside the review time frame, and another (Inestia et al, 2022) was excluded as explained above.

9. Annex C: Independent report of expert statistician

Traffic Light System for Treatment Add-ons: Microbiome testing

Zipporah Iheozor-Ejiofor, April 2026

INTRODUCTION

The HFEA website provides patients with digestible information on treatment add-ons in the form of a rating system. The purpose of this report is to inform the HFEA's Scientific and Clinical Advances Advisory Committee's (SCAAC) deliberations on updating this information. In particular, this update extends the ratings system to cover microbiome testing.

The aim of the work reported below is to critically appraise, interpret and summarise, for consideration by SCAAC, the reports of identified studies.

METHOD

Rebecca Taylor, provided references and hyperlinks to identified studies for consideration, categorised by add-on, study design and population under study. I screened and prioritised the studies, including checking of author names against the retraction watch database.

Critical review of studies included assessment of risk of bias from allocation method, blinding, selective reporting, unexplained attrition, unplanned interim analysis and other miscellaneous errors in the design, conduct or reporting of results. To classify a randomised trial as providing moderate/high quality evidence I have applied the default classification of the Cochrane Gynaecology and Fertility review group. Specifically, for a study to be considered in this category it must describe an adequately concealed randomisation process to prevent selection bias. It must also not be identified as at high risk of bias in other regards ('unclear' is acceptable) other than where blinding is unrealistic. Where HFEA specifically requested results for a sub-population of interest, I have presented first the studies addressing the general population and then studies addressing the specific sub-populations. The extent to which interpretation of sparse results for a sub-population should borrow from the broader information available is addressed on a case-by-case basis.

To calculate odds ratios, published results were re-calculated applying the intention to treat (ITT) principle where possible and using two-sided confidence intervals. As these were being interpreted as indicative rather than inferential, no technical adjustments were applied for multiple testing, covariate adjustment or planned interim analyses. For studies where possible, odds ratios were calculated for the latest clinical outcome presented. That is, live birth rate was first choice, followed by ongoing, clinical, unspecified or biochemical pregnancy. An odds ratio greater than 1.0 for these outcomes implies benefit of the add-on under study. Additional outcomes as requested by HFEA are presented with confidence intervals based on reported means and standard deviations. A difference greater than zero implies a higher mean for the intervention group.

RESULTS

1. *Microbiome testing*

The references of 27 studies (published in 28 articles) were provided for consideration. Of these 27 studies, two were excluded for including couples who were trying to conceive naturally (Fernandez 2021) and not including a control group (Iniesta 2022). Twenty five studies were included - seven RCTs, five systematic reviews and 13 non-randomised studies. The studies assessed a general population receiving needed artificial reproductive treatment (Di Pierro 2023, Eskew 2021, Hanaoka 2025, Raimondo 2025, Tanha 2023, Thanaboonyawat 2023, Wei 2024), women with abnormal microbiome (Haahr 2025, Irollo 2017), chronic endometritis (Cicinelli 2015, Hu 2024, Kitaya 2017, Liu 2022, Xiong 2021) and recurrent implantation failure (Kamrani 2025, Iwami 2022, Iwami 2025, Zou 2023). The study participants underwent microbiome testing of vaginal or endometrial samples to determine the microbial profile of the uterine cavity and this was followed by an intervention such as antibiotics, probiotics or a combination of both.

1 (i) *General population*

Seven studies were identified that included a general population of patients undergoing assisted reproduction.

These studies were published between 2019 and 2025. There are three RCTs (Tanha 2023, Thanaboonyawat 2023, Eskew 2021) and four non-randomised studies (Wei 2024, Raimondo 2025, Di Pierro 2023 and Hanaoka 2023). The studies assessed women with infertility aged 18 to 49 years. Study participants received probiotics orally or vaginally for 6 to 30 days (Tanha 2023, Thanaboonyawat 2023, Eskew 2021, Wei 2024, Raimondo 2025, Di Pierro 2023, Hanaoka 2025). Antibiotics were administered in two studies (Hanaoka 2025, Eskew 2021) based on what the pathogens are known to be susceptible to.

All studies except two (Tanha 2023, Thanaboonyawat 2023) were at high risk of bias due to lack of allocation concealment and lack of blinding. In Hanaoka 2025, there was 33% attrition rate and Raimondo 2025 did not use number of cycles as the denominator thus distorting the outcome estimation.

Live birth was reported in five studies. It is uncertain whether probiotic improves live birth as the quality of evidence is very low (OR 1.32 [95% CI 0.9 to 1.93]; n = 970 participants; 4 studies). The evidence was downgraded due to lack of allocation concealment, indirectness and imprecision due to low number of events. It is uncertain whether antibiotics improve live birth due to very low certainty evidence from one study (Eskew 2021) (OR 0.48 [95% CI 0.10 to 2.23]; n = 27 participants; 1 study).

It is uncertain whether antibiotics improve ongoing pregnancy in infertile women as the quality of the evidence is very low (Hanaoka 2025) (OR 0.92 [95% CI 0.45 to 1.86]; n = 170 participants; 1 study)

Four studies reported no clear difference in clinical pregnancy when probiotic was compared to control (OR 1.51 [95% CI 0.98 to 2.32]; n = 663 participants). An additional study (Jafarabadi 2024) which was not included in the meta-analysis also found no difference between probiotics and no treatment (RR: 1.14, 95% CI: 0.76 to 1.74; p = 0.623, n = 166 participants).The evidence was rated low quality due to the lack of allocation concealment across the studies and wide confidence intervals. Similar results were reported in studies which compared antibiotics with control (OR 1.02 [0.55 to 1.90]; n = 197 participants; 2 studies).

Miscarriage was reported in five studies. Overall, the studies showed no clear difference in miscarriages between probiotics and control (OR 0.67 [95% CI 0.38 to 1.17]; n = 971 participants; 4 studies). The quality of the evidence was low due to lack of allocation concealment and indirectness of the outcome data assessed per cycle. It is uncertain whether antibiotics prevent miscarriages as the quality of the evidence is uncertain (OR 4.04 [95% CI 0.15 to 108.57]; n = 27 participants; 1 study)

Recommendation:
Grey for Live birth
Grey for ongoing pregnancy
Grey for clinical pregnancy
Grey for miscarriage

1 (ii) Recurrent implantation failure

Five studies were identified that included people with recurrent implantation failure undergoing assisted reproduction (Kamrani 2025, Jafarabadi 2024, Iwami 2022, Iwami 2025, Zou 2023). Two of the studies were RCTs and the other three were NRSIs. The participants were between the ages of 18 and 41 with >=3 implantation failures from previous cycles.

Four of the studies (Kamrani 2025, Jafarabadi 2024, Iwami 2022, Iwami 2025) assessed the effectiveness of probiotics with or without antibiotics and one study (Zou 2023) assessed antibiotics alone. When the studies were assessed for risk of bias, only one study used appropriate allocation concealment (Jafarabadi 2024) and one study attempted blinding (Kamrani 2025). There was no selective reporting, high levels of attrition or imbalance in reasons for attrition.

Low quality evidence from one study (Iwami 2022) suggests probiotic plus antibiotic may improve live birth compared to no treatment (OR 4.89 [95% CI 1.96 to 12.21]; n = 195 participants). However, the evidence is low quality due to high risk of bias and imprecision.

Two studies assessed antibiotics (Zou 2023) and probiotics with/without antibiotics (Iwami 2025). It was not feasible to combine data from the studies in a single analysis due to the heterogeneity of the interventions. Although the studies suggest that the interventions may be improve ongoing pregnancy, none of the results were statistically significant. Iwami 2025 compared probiotic with antibiotics (OR 1.02 [95% CI 0.65 to 1.61], n = 339 participants) and probiotic (OR 1.08 [95% CI 0.73 to 1.59], n = 417 participants) with control while Zou 2023 compared antibiotics with control (OR 2.21 [95% CI 0.67 to 7.23]; n = 141 participants).

Of the four studies reporting on clinical pregnancy, only two were considered sufficiently similar in terms of intervention assessed. Kamrani 2025 and Iwami 2025 compared probiotic to no treatment. The meta-analysis found that probiotic may improve clinical pregnancy in women with recurrent implantation failure (OR 3.57 [95% CI 2.42 to 5.27]; n = 467 participants; 2 studies). The evidence was downgraded to low quality due to high risk of bias. Similarly, evidence from two studies suggests that probiotics plus antibiotics may also improve clinical pregnancy in women with RIF when compared to control (OR 3.51 [95% CI 2.24 to 5.5]; n = 534 participants). The evidence was downgraded to low quality due to high risk of bias from both studies.

When miscarriage was assessed, there were three studies that were eligible for the analysis. However, only the two studies (Iwami 2022 and Iwami 2025) could be meta-analysed. It is uncertain whether probiotics plus antibiotics can prevent miscarriages in women with RIF as the quality of evidence is very low (OR 1.32 [0.4 to 4.33], n = 534 participants, 2 studies). There is insufficient evidence from two studies to determine whether probiotics alone (OR 0.39 [95% CI 0.14 to 1.09], n = 417 participants) or antibiotics alone (OR 0.68 [95% CI 0.14 to 3.36], n = 141 participants) can prevent miscarriage in women with RIF.

Recommendations on probiotic plus antibiotics:
Live birth/Ongoing pregnancy: Grey
Clinical pregnancy: Grey
Miscarriage: Grey

Justification: Probiotic plus antibiotics appeared to improve live birth and clinical pregnancy. The evidence on live birth is from a single study with small sample size and this increased the uncertainty of the evidence. Probiotic alone also improves clinical pregnancy. Live birth data was not analysed with ongoing pregnancy due to considerable heterogeneity which would have increased inconsistency.

1 (ii) *Abnormal microbiome*

Two RCTs were identified that included women with abnormal microbiome undergoing assisted reproduction. The participants were 30 to 35 years old women with intestinal dysbiosis in one study (Irollo 2017) while the other study participants had abnormal vaginal microbiota (Haahr 2025). Haahr 2025 compared probiotic plus antibiotics with antibiotics and placebo while Irollo 2017 compared probiotic with no probiotic. Haahr 2025 had low risk of bias while Irollo 2017 had high risk of bias. It was not feasible to meta-analyse the results due to the differences in interventions.

Low quality evidence from one study suggests that antibiotics may improve live births in women with dysbiosis compared to placebo (OR 4.46 [95% CI 2.56 to 7.8], n = 227 participants, 1 study). The evidence was downgraded due to imprecision. It is uncertain whether probiotic (OR 8.67 [95% CI 2.06 to 36.51], n = 53 participants, 1 study) improves live birth in women with dysbiosis as the quality of evidence is very low. When probiotics plus antibiotics were compared with placebo, there was no clear difference in live births (OR 1.18 [95% CI 0.67 to 2.07], n = 227 participants, 1 study).

Haahr 2025 reported on clinical pregnancy and found no differences when antibiotic with probiotic (OR 1.08 [95% CI 0.55 to 2.13]) or antibiotics alone (OR 1.14 [95% CI 0.58 to 2.23]) were compared with placebo. The evidence was downgraded for imprecision.

Recommendations

Live birth/Ongoing pregnancy: Grey
Clinical pregnancy: Grey

Justification: Antibiotics and probiotic as single therapies appear to improve live birth in women with dysbiosis, however, there is uncertainty around the evidence as it is based on single small studies.

1 (ii) *Chronic endometritis*

Five studies were identified that included women with chronic endometritis undergoing assisted reproduction (Hu 2024, Liu 2022, Xiong 2021, Cicinelli 2015, Kitaya 2017). Overall, the studies included participants were >=42 years diagnosed with chronic endometritis, however, Liu 2022 made further distinction in participants based on the severity of their condition (low and high grade). Two studies (Xiong 2021, Kitaya 2017) compared antibiotics with no treatment, one study (Hu 2024) compared antibiotics plus probiotic with antibiotics alone and another study (Cicinelli 2015, Liu 2022) compared long term use of antibiotics to short term use of antibiotics.

The studies were all at high risk of bias due to lack of randomisation/allocation concealment and blinding. There was no attrition or selective reporting except for Hu 2024 where early miscarriage was reported instead of miscarriage. Cicinelli 2015 only reported the outcome data as percentages, therefore, this was considered selective reporting.

Due to the heterogeneity of the interventions, it was only possible to meta-analyse two studies (Kitaya 2017, Xiong 2021). Low quality evidence from 659 participants showed no clear difference in live births (OR 1.35 [95%CI 0.96 to 1.89]), clinical pregnancy (OR 1.24 [95% CI 0.79 to 1.93]) or miscarriages (OR 1.08 [95% CI 0.56 to 2.1])) when antibiotics were compared to no treatment in women with chronic endometritis. The evidence is rated low due to high risk of bias and imprecision.

In contrast, the results were mixed when short term and long term antibiotic therapy were compared. One study (Cicinelli 2015) with 61 participants reported a difference in live birth (61% vs. 13%; p = 0.02) and clinical pregnancy (65% vs. 33%; p = 0.039) in favour of the short term antibiotics therapy group. However, it found no clear difference in miscarriage (5% vs. 10%; p = not significant) between short and long term antibiotics therapy. The evidence was downgraded to low quality due to high risk of bias.

Based on very low quality evidence from one study (Liu 2022), it is uncertain whether there is a difference in live birth, clinical pregnancy and miscarriage when short term and long term antibiotic therapy are compared in women with low grade and high grade chronic endometritis. Hu 2024 found no difference in live birth or miscarriage when antibiotics plus probiotic was compared to antibiotics alone.

Recommendations

Live birth/Ongoing pregnancy: Grey
Clinical pregnancy: Grey
Miscarriage: Grey

Justification: Most of the results are not statistically significant and those that are statistically significant either have wide confidence intervals or small sample sizes. Given that all the studies are also at high risk of bias, it is uncertain whether antibiotics (with or without probiotics) improve live birth, clinical pregnancy and miscarriage.

COMPARISON WITH PREVIOUS REVIEWS

Four systematic reviews and a synthesis of expert opinion were available. However, they do not add new knowledge to the findings of these primary studies.

DISCUSSION

Caution is required as the assessments above are made from a methodological perspective without expertise in the clinical or scientific context. It is worth noting that it is not uncommon for a trial to be well-designed to answer a question of little clinical value.

The recommendations for rating are intended only as a starting point for committee discussion.
Some comparisons contain a range of interventions (e.g. varied quantity, timing and duration of dose) in populations defined by different eligibility criteria. Alternative post-hoc but biologically plausible rationales could be put forward to ‘lump’ or further ‘split’ categories presented above.

REFERENCES: Reviewed studies

Adjunct		Study	DOI/reference
Probiotic			
ART		Di Pierro 2023	https://www.mdpi.com/2076-2607/11/11/2796
		Hanaoka 2025	https://doi.org/10.1007/s10815-025-03759-0
		Irollo 2017	https://doi.org/10.4081/jsas.2017.7883
		Jafarabadi 2024	https://doi.org/10.18502/ijrm.v22i5.16435
		Kamrani 2025	https://doi.org/10.1016/j.humimm.2024.111220
		Raimondo 2025	https://doi.org/10.3390/nu17030410
		Tanha 2023	https://doi.org/10.1007/s00404-023-07147-w
		Thanaboonyawat 2023	https://doi.org/10.1038/s41598-023-39078-6
		Wei 2024	https://doi.org/10.1007/s10815-024-03066-0
Probiotic antibiotics	with/without	Iwami 2022	https://doi.org/10.1007/s10815-022-02688-6
		Iwami 2025	https://doi.org/10.1002/rmb2.12634
		Haahr 2025	https://doi.org/10.1038/s41467-025-60205-6
		Hu 2024	https://doi.org/10.3389/fcimb.2024.1494931
Antibiotics			https://doi.org/10.1093/humrep/deu292
		Cicinelli	https://doi.org/10.1016/j.xfss.2021.01.002
		Eskew 2021	https://doi.org/10.1007/s10815-025-03759-0
		Hanaoka 2025	https://doi.org/10.1111/aji.12719
		Kitaya 2017	https://doi.org/10.1111/aji.13669
		Liu 2022	https://doi.org/10.1016/j.fertnstert.2021.03.036
		Xiong 2021	https://doi.org/10.1016/j.jri.2022.103782
		Zou 2023	

Rating review for treatment add-ons – Sperm DNA fragmentation testing

Details about this paper

Area(s) of strategy this paper relates to:	Regulating a changing environment
Meeting:	Scientific and Clinical Advances Advisory Committee (SCAAC)
Agenda item:	8
Paper number:	HFEA (03/06/2026) 008
Meeting date:	3 June 2026
Authors:	Rebecca Taylor, Scientific Policy Manager
Annexes	Annex A: Evidence decision tree for rating add-ons Annex B: References - studies considered but not included in rating review Annex C: Expert statisticians' independent report

Output from this paper

For information or recommendation?	For recommendation
Recommendation:	Members are asked to: • consider the quality of evidence for the use of sperm DNA fragmentation testing and arising recommendations as a treatment add-on based on the findings from an independent assessor; • agree and recommend ratings for each outcome(s) and population(s); • consider how the ratings might be presented to the public on the HFEA website.
Resource implications:	In budget
Implementation date:	Recommendations will be implemented as soon as feasible
Communication(s):	Updates to the HFEA's website information on treatment add-ons and communication of updates to the sector, patients and public.

Organisational risk:	Low

1. Background

1.1. Treatment add-ons are often non-essential treatments or tests that may be offered in fertility clinics in addition to routine treatment with the claim that they can improve treatment outcomes.

1.2. Tests were added to the add-on definition in July 2025, following a proposal from the SCAAC which was agreed by the Authority (**see minutes**).

1.3. In relation to tests, it was not expected that the HFEA would undertake a review on the accuracy of the testing, but the impact on fertility treatment outcomes of recommended action arising from test results.

1.4. As with all new treatments, tests or technologies being introduced into reproductive medicine, the HFEA expect the introduction of treatment add-ons into clinics to be preceded by good quality scientific research into the effectiveness and safety of these interventions. However, some treatment add-ons are being offered to patients despite a lack of evidence for effectiveness at increasing live birth rate, improving safety, or other treatment outcomes such as reducing the chance of miscarriage. They are frequently offered outside of a research setting and are subject to additional costs for the patient.

1.5. HFEA and eight professional and patient bodies have committed to encourage responsible innovation and offering of treatment add-ons in UK clinics in a **consensus statement**.

1.6. Medical professionals, academics or patient organisations can propose that we review the evidence base for a treatment or test add-on if they are concerned that it is being offered to patients in a UK licensed clinic:

- with the claim that it will increase the live birth rate or improve other treatment outcomes;
- without conclusive evidence of its effectiveness at improving the live birth rate or other treatment outcomes;
- it is not already listed in our the HFEA's rated list of add-ons; or
- there is evidence that an add-on treatment or test may reduce treatment effectiveness or there are potential safety concerns.

1.7. Sperm DNA fragmentation testing as an add-on arose in discussions at the June 2025 SCAAC meeting (**see minutes**). At the meeting, SCAAC members recommended that, subject to a small change in the definition of add-on being approved by the Authority, sperm DNA fragmentation testing should be rated as an add-on.

1.8. An add-on review panel took place on 10 November 2025. The panel agreed that:

The populations of interest were:

- Male – general fertility patient population (will include unexplained male infertility, male factor fertility, varicocele)
- Female – recurrent miscarriage (RPL – repeated pregnancy loss)

The outcomes of interest were:

- Live birth
- (if live birth not available) ongoing pregnancy rate and/or clinical pregnancy rate
- Miscarriage rate

The panel also noted the following:

- Some NSRIs may look at very specific patient sub-groups.
- Male patients' exposure to radiation or endocrine disruptors and genital tract inflammation may be considered at a later stage.

2. Literature search – updated process

2.1. The MEDLINE (Ovid) database, along with two clinical trial registries in line with Cochrane (International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov) were used to carry out the literature search[1].

2.2. The literature search first identified relevant randomised controlled trials (RCTs) and systematic reviews. While the search identified 18 RCTs, most were not directly comparable as they were looking at slightly different interventions. For example, there were nine RCTs looking at antioxidants or other supplements, but the supplements/antioxidants had slightly different compositions:

- Four looked at supplements containing L-carnitine, but other ingredients were not identical.
    - Three looked at folic acid, although one combined folic acid with zinc.
    - Two looked at Alpha-Lipoic Acid, one of which combined ALA with L-carnitine (the latter is also included in the four L-carnitine studies above)
    - One looked at N-acetyl-L-cysteine (NAC) supplementation post varicocelectomy

- There were three RCTs looking at different permutations of IVF:
    - One study looking at IVF outcomes following sperm selection by MACS (magnetic cell-sorting sperm selection) or TESA
    - One study comparing PICSI vs ICSI using MACS
    - One study comparing ICSI with density gradient centrifugation (DGC) to testicular sperm ICSI, PICSI and ICSI with MACS.

2.3. The search was therefore expanded to non-randomised studies of intervention (NRSIs) which are limited to case/cohort/control studies. 14 NSRIs were identified:

- 11 studies compared different permutations of IVF for men with high SDF such as ICSI using ejaculated sperm vs ICSI using testicular sperm (nine studies) alongside one study comparing multiple variations of ICSI, one study comparing IUI, IVF and ICSI.
- Two studies comparing magnetic cell sorting sperm selection (MACS) with density gradient centrifugation (DGC)
- One study looking at the impact of ART timing on ICSI treatment for patients with high SDF.

[1] In line with the decision tree found at Annex A, neither pre-prints nor abstracts are included in the evidence base.

2.4. At the February 2017 SCAAC meeting, it was agreed that evidence published in the last 10 years would be sent for review. The literature search covered the period of February 2016 to February 2026. The studies found date from 2016 to 2025.

3. Independent assessment of the quality of evidence

3.1. In order to categorise the treatment add-ons under consideration, it is necessary not only to identify the published evidence on each treatment add-on, but also to assess the quality of that evidence. For this reason, we seek advice from an expert in systematic reviews and evidence assessment to carry out an independent assessment of the quality of evidence (using the GRADE methodology[2]) for each treatment add-on.

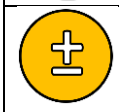
3.2. The critical review of studies included assessment of risk of bias from allocation method, blinding, selective reporting, unexplained attrition, unplanned interim analysis and other miscellaneous errors in the design, conduct or reporting of results. However, the assessments made by the independent reviewer are from a methodological perspective without expertise in the clinical or scientific context.

3.3. Findings of the independent assessment for sperm DNA fragmentation testing can be found in Annex C, the report of the external expert statistician. This report details the independent reviewers recommended rating in relation to the HFEA's five-category rating system, along with the studies used in the assessment. Other studies that were considered, but not used in the assessment are listed in Annex B.

4. The five-category rating system

4.1. The decision tree for determining how evidence will be used by SCAAC when assigning add-ons rating can be found at Annex A.

4.2. The Authority approved a five-category rating system with the following symbols/colours and definitions in July 2022:

	On balance, findings from high quality evidence shows this add-on **is effective at improving the treatment outcome**.
	On balance, it is **not clear whether this add-on is effective at improving the treatment outcome**. This is because there is conflicting moderate/high quality evidence – in some studies the add-on has been found to be effective, but in other studies it has not.
	**We cannot rate the effectiveness of this add-on at improving the treatment outcome** as there is insufficient moderate/high quality evidence.
	On balance, the findings from moderate/high quality evidence shows that **this add-on has no effect on the treatment outcome**.

[2] GRADE is an approach for grading the quality of evidence and the strength of recommendations. It was developed by the Grading of Recommendations, Assessment, Development and Evaluation Working Group.

	There are **potential safety concerns and/or**, on balance, the findings from moderate/high quality evidence shows that **this add-on may reduce treatment effectiveness**.

4.3. Most treatment add-ons on our website will have a rating to indicate whether the evidence shows that the treatment add-on is effective at improving the chances of having a baby for most fertility patients. However, as approved by the Authority, the five-category rating system may also be applied to additional outcomes, such as miscarriage, and outcomes for specific patient groups, such as those diagnosed with male-factor infertility.

5. Considerations and recommendations for rating sperm DNA fragmentation testing and recommended interventions arising from testing

5.1. Sperm DNA fragmentation sometimes referred to as sperm DNA damage occurs when the generic material (DNA) within sperm is damaged. Sperm DNA damage is assessed by tests that measure the DNA fragmentation index (DFI). A DFI below 15% is generally considered normal, while higher levels have been associated with reduced fertility and increased risk of miscarriage, although the evidence is inconclusive.

5.2. There are no agreed thresholds for defining elevated sperm DNA fragmentation, however a commissioned review published in Andrologia in 2020 (Esteves et al, 2020 "**Sperm DNA fragmentation testing: Summary evidence and clinical practice recommendations**") did make some recommendations on SDF thresholds:

- Thresholds of about 20% by TUNEL, SCSA, SCD and alkaline Comet tests best discriminate fertile from infertile men.
- Thresholds of 20%–30% evaluated by SCSA, alkaline Comet and SCD are clinically useful for classifying infertile couples into a statistical probability of longer time to achieve natural pregnancy, decreased chances of pregnancy by IUI, IVF and ICSI, and increased miscarriage risk.

5.3. There is information on sperm DNA damage **on the HFEA website**, which also lays out our position on testing:

- "Several different tests might be used by your clinic to assess the level of DNA damage in your sperm. There is some evidence for a relationship between sperm DNA damage and the outcome of fertility treatment. However, the evidence is conflicting and depends on the type of test used by the clinic. The results of a sperm DNA damage test are unlikely to impact on the management of your treatment."

5.4. The new NICE fertility guideline includes recommendations on sperm DNA fragmentation testing and an **evidence review** of it. NICE's recommendations in relation to managing sperm DNA fragmentation include:

- 1.17.6 "Do not carry out testing for sperm DNA integrity (fragmentation)".
- 1.24.6 "Do not offer supplements, antioxidants or medical treatments to improve sperm DNA integrity (fragmentation)."

- 1.27.1: “Do not offer surgical sperm retrieval as a way to improve outcomes for men, and trans women and non-binary people with male reproductive organs who have non-azoospermia and reduced sperm DNA integrity (elevated fragmentation levels).”

5.5. NICE’s conclusion is that sperm DNA fragmentation testing has not been proven to show benefit and that there are many uncertainties with how the tests are undertaken and interpreted. Specifically:

- In relation to NICE recommendation 1.17.6: “The evidence on treating sperm DNA fragmentation did not show a convincing benefit. Without effective treatments, and given that sperm DNA assays are expensive tests that can take weeks to obtain results, the committee recommended against testing for sperm DNA integrity (fragmentation). They agreed that the link between elevated DNA fragmentation and subfertility has not yet been established. It is also not clear which type of test and what threshold should be used for defining elevated DNA fragmentation. Given these uncertainties, the committee agreed that testing for sperm DNA integrity is not appropriate”.
- In relation to NICE recommendation 1.24.6: “There was no standardised treatment for sperm DNA fragmentation with different types, doses and combinations of antioxidants, supplements and medical treatments used across studies, and no convincing evidence of benefit because antioxidants showed equivocal effects on live birth and sperm DNA fragmentation. There were also no benefits in relation to clinical pregnancy, miscarriage, stillbirth, and embryo quality or grading. The committee agreed that currently there is too much uncertainty about the relationship between sperm DNA fragmentation and subfertility, about the best way to test and define this, and if and how this should be treated. Before these uncertainties are resolved, they agreed that testing and treating sperm DNA integrity is not appropriate.”
- In relation to NICE recommendation 1.27.1: “There was limited evidence on testicular sperm extraction as a treatment for sperm DNA fragmentation, and no benefits were shown in terms of pregnancy or miscarriage rates when comparing ICSI using extracted sperm and ICSI using ejaculated sperm. The committee also acknowledged the wider uncertainties about the relationship between sperm DNA fragmentation and subfertility, and the best way to test and define this. Based on this evidence, the committee recommended against surgical sperm retrieval as a way of improving outcomes for people with reduced sperm DNA integrity.”

5.6. There is some crossover of studies in the NICE evidence review and those found by our literature search, so some are included in the report in annex D.

5.7. ESHRE’s 2023 **Good practice recommendations on add-ons in reproductive medicine** do not recommend using SDF testing, noting:

- “There is insufficient evidence for the relevance of SDF tests to predict pregnancy or guide treatment decisions. Further research in this field is strongly recommended to enhance our understanding and knowledge.”

5.8. The 2025 update of the European Association of Urology **Guidelines on Male Sexual and Reproductive Health** addressed sperm DNA fragmentation and made the following recommendations:

- Perform SDF testing in the assessment of couples with recurrent pregnancy loss from natural conception and failure of ART and for men with unexplained infertility (Strong recommendation)
- Consider the use of testicular sperm for ICSI in patients with high SDF in ejaculated sperm as an experimental option (Weak recommendation)
- Varicocelectomy may be considered in men with elevated sperm DNA fragmentation with otherwise unexplained infertility and men with failure of assisted reproductive techniques, including recurrent pregnancy loss and failure of embryogenesis and implantation (Weak recommendation)

5.9. UK fertility charity **Chana**, which supports couples going through fertility treatment and in some cases provide funding, do not recommend or fund fertility treatment add-ons. However, in relation to sperm DNA fragmentation testing, the charity will agree to fund sperm DNA fragmentation testing for couples who experience failed rounds of IVF with embryos considered good quality without an obvious cause, or those who have had recurrent early pregnancy loss. The rationale for this is that should the testing reveal a high level of DNA damage, then the couple can be advised to visit a urologist to see if there is a reason for the test results. Depending on the outcome of urology examinations, further advice may be given such as lifestyle changes or undertaking ICSI for any subsequent rounds of treatment. Without the testing, it is possible that the couple would undertake further failed rounds of IVF creating distress, disappointment and additional costs. Further information on Chana's position on SDF testing can be found **here**.

5.10. UK registered fertility clinics market SDF testing in a number of ways including:

- For specific indications including unexplained fertility, recurrent miscarriage and repeated IVF/ICSI failure:
  - **HCA Healthcare UK website** says that sperm DNA testing "helps uncover hidden causes of subfertility or miscarriage".
  - **King's Fertility** say they sometimes recommend it for "unexplained infertility, recurrent miscarriage and failed IVF cycles".
  - **Concept Fertility** say that testing can be helpful "in cases of unexplained infertility, recurrent miscarriage, or repeated unsuccessful treatment cycles – especially when standard semen analysis appears normal".
- As going beyond routine semen analysis:
  - The **Forbury Clinic website**: says that "in many cases standard sperm analysis alone does not tell the full story".
  - **IVF Matters** offer two male fertility testing packages that including sperm DNA analysis, with one just noting that it "checks the quality of the genetic material within the sperm"

5.11. There are also other providers that market DNA sperm fragmentation tests:

- **Fertility Solutions** which offer fertility testing and market SDF tests as “the go-to assessment to understand a man’s fertility on a deeper level” and say they perform it as standard.
- **The Male Fertility Clinic**, which offers SDF testing noting that it “Checks sperm DNA quality, crucial for conception and reducing the chances of miscarriage”.
- **Marylebone Diagnostic Centre** say SDF testing can “provide deeper insight into male fertility”.

5.12. There are a number of sperm DNA fragmentation tests that are commonly offered by fertility clinics or other providers:

- **Examen (Exact/SpermComet)**
- **Halosperm (SCD test)**
- **SCSA (sperm chromatin structure assay**)
- TUNEL (terminal deoxynucleotidyl transferase dUPT nick end labelling) assay. There are several manufacturers of this test including **Thermo Fisher Scientific**, **R&D Systems** and **Abcam**.

Expert review April 2026

GREY for improving live birth for patients undergoing treatment due to male factor infertility

Clinical studies looking at interventions to treat men with high sperm DNA fragmentation (above 20%) were reviewed. The studies were of highly variable quality with inconsistent results for all outcomes. Interventions included:

- Different formulations of antioxidants - ingredients included alpha lipoic acid, folic acid, N-acetyl-L-cysteine, L-carnitine, lycopene, vitamins B, C & E, zinc, selenium, coenzyme Q10
- Different sperm selection techniques – ICSI (intracytoplasmic sperm injection), MACS (magnetic activated cell sorting), PICSI (physiological intracytoplasmic sperm injection), DGC (density gradient centrifugation), testicular sperm retrieval including TESA (testicular sperm aspiration)
- Ejaculatory abstinence

GREY for patients undergoing treatment due to male factor infertility

- improving clinical pregnancy rate and/or ongoing pregnancy rate; and
- reducing miscarriage rate.

Clinical studies looking at interventions to treat men with high sperm DNA fragmentation (above 20%) were reviewed (see details under live birth rate above), but overall the studies were of highly variable quality with inconsistent results for all outcomes.

GREY for patients with recurrent pregnancy loss (RPL) for

- for improving live birth;
- improving clinical pregnancy rate and/or ongoing pregnancy rate; and
- reducing miscarriage rate.

There were no studies specifically addressing patients who had experienced recurrent pregnancy loss.

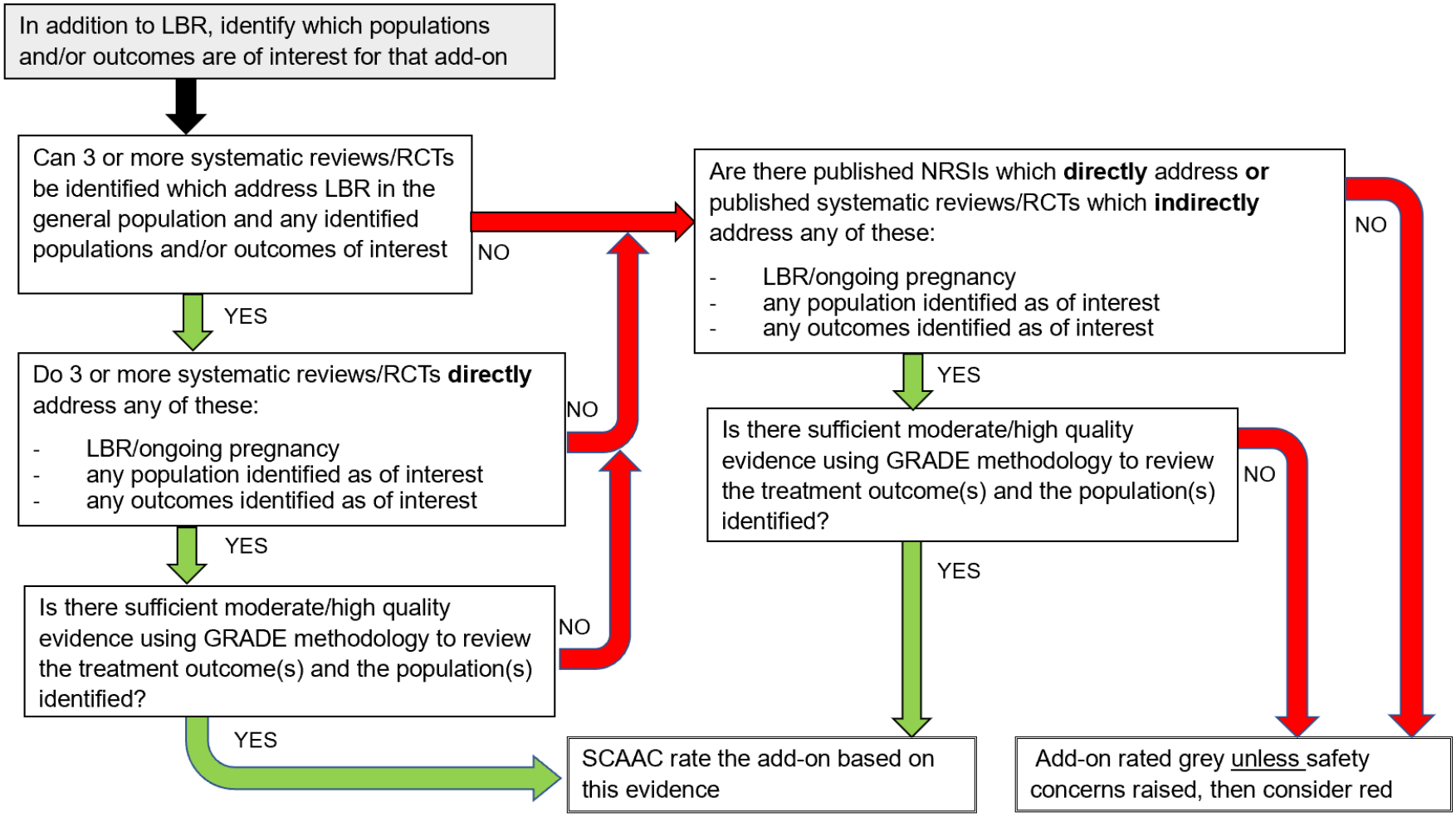
6. Recommendations

6.1.

Members are asked to:

- consider the quality of evidence for sperm DNA fragmentation testing as a treatment add-on based on the findings from an independent assessor;
- agree and recommend ratings for each outcome(s) and population(s);
- consider how the ratings might be presented to the public on the HFEA website, for example the level of detail on different interventions and sub-groups arising from the studies.

7. Annex A: Evidence decision tree for rating add-on



8. Annex B: References – studies considered but not included in rating review

The studies used in the rating review are listed in the expert report (Annex C). Some other studies were provided for consideration, but were not used in the rating review. They were as follows:

- Esteves et al (2023), **https://dx.doi.org/10.1111/andr.13405** – NSRI not used in the rating review as sufficient RCTs were available.
- Esteves et al (2017), **https://doi.org/10.1016/j.fertnstert.2017.06.018** - NSRI not used in the rating review as sufficient RCTs were available.
- Gamidov (2019) – excluded because the article was published in Russian with only an abstract available in English.
- Huang et al (2019) **https://doi.org/10.1111/andr.12652** - excluded because outcomes were not reported in a useable format.
- Khoo et al (2024) **https://doi.org/10.1016/j.euf.2023.08.008** – This article is a systematic review and meta analysis; studies from this review were used in the add-on review.
- Schisterman et al (2020), **https://doi.org/10.1093/aje/kwz217** - This article does not report study data and findings. A later article of this study which included data and findings was included in the rating review.

9. Annex C: Independent report of expert statistician

Traffic Light System for Treatment Add-ons: Sperm DNA fragmentation testing add-on review
Arun Kumar, April 2026

INTRODUCTION

The HFEA website provides patients with digestible information on treatment add-ons in the form of a rating system. The purpose of this report is to inform the HFEA's Scientific and Clinical Advances Advisory Committee's (SCAAC) deliberations on updating this information. In particular, this update extends the ratings system to cover sperm DNA fragmentation testing.

The aim of the work reported below is to critically appraise, interpret and summarise, for consideration by SCAAC, the reports of identified studies.

METHOD

Rebecca Taylor, provided references and hyperlinks to identified studies for consideration, categorised by add-on, study design and population under study. I screened and prioritised the studies, including checking of author names against the retraction watch database.

Critical review of studies included assessment of risk of bias from allocation method, blinding, selective reporting, unexplained attrition, unplanned interim analysis and other miscellaneous errors in the design, conduct or reporting of results. To classify a randomised trial as providing moderate/high quality evidence I have applied the default classification of the Cochrane Gynaecology and Fertility review group (GRADE methodology). Specifically, for a study to be considered in this category it must describe an adequately concealed randomisation process to prevent selection bias. It must also not be identified as at high risk of bias in other regards ('unclear' is acceptable) other than where blinding is unrealistic. Where HFEA specifically requested results for a sub-population of interest, I have presented first the studies addressing the general population and then studies addressing the specific sub-populations. The extent to which interpretation of sparse results for a sub-population should borrow from the broader information available is addressed on a case-by-case basis.

To calculate odds ratios, published results were re-calculated applying the intention to treat (ITT) principle where possible and using two-sided confidence intervals. As these were being interpreted as indicative rather than inferential, no technical adjustments were applied for multiple testing, covariate adjustment or planned interim analyses. For studies where possible, odds ratios were calculated for the latest clinical outcome presented. That is, live birth rate was first choice, followed by ongoing, clinical, unspecified or biochemical pregnancy. An odds ratio greater than 1.0 for these outcomes implies benefit of the add-on under study. Additional outcomes as requested by HFEA are presented with confidence intervals based on reported means and standard deviations. A difference greater than zero implies a higher mean for the intervention group.

RESULTS

1. Sperm DNA fragmentation

The current search identified a total of 28 primary research studies. Hand searching identified one further randomised study for consideration. Priority for this report is given to the 11 randomised trials. The 4

systematic reviews were largely based on observational studies and where RCTs were included they were either older studies or did not report any outcomes of interest. The remaining primary studies were not prioritised as they were predominantly retrospective or observational, and sufficient RCT evidence was available.

The included RCTs (n=11) were published between 2016 and 2024 and conducted across 8 countries: Egypt (n=2), United States (n=2), Iran (n=2), and one each in India, France, Turkey, Sweden, and Tunisia. Study recruitment ranged from 2011 to 2022, with most trials conducted between 2015 and 2020.

Two additional RCTs were considered for inclusion but were excluded on the basis that Gamidov (2019) was a Russian-language article with only an English abstract available, and outcomes in Huang (2019) were not reported in a usable format (i.e. they were presented by genotype subgroups, with participants potentially included in more than one group).

1 (i) *General population - Male*

11 studies were identified that included a general male population undergoing assisted reproduction, including 7 studies on antioxidants, 3 on sperm selection techniques, and 1 on ejaculatory abstinence.

Antioxidants

Barekat 2016 randomised 40 men with primary infertility and left-sided varicocele (grade II–II, I) undergoing varicocelectomy to receive post-operative N-acetyl-L-cysteine or no post-varicocelectomy treatment. This was a small RCT with high risk of bias. Clinical pregnancy was higher in the N-acetyl-L-cysteine group 5/20 (25%) versus no post-varicocelectomy treatment 2/20 (10%), however this was not statistically significance (RR 2.5 (0.55 to 11.41)).

Habibi 2022 randomised 70 men with infertility and high sperm DNA fragmentation (≥15% TUNEL or ≥30% SCSA) to alpha-lipoic acid (ALA) (600 mg/day) or placebo for 80 days in a randomised triple-blind placebo-controlled clinical trial. The study was at high risk of bias due to differential attrition between groups (Placebo 17% vs 2.8%). Clinical pregnancy was higher in the intervention group (23.5% vs 10.3%), however this was not statistically significant (p=0.169).

Lahimer 2023 randomised 263 men with male factor infertility and high sperm DNA fragmentation (≥20% TUNEL) to receive oral antioxidants (L-carnitine plus a micronutrient combination) or placebo for 3 months prior to assisted reproductive techniques. There were some concerns regarding overall risk of bias as no information on allocation sequence concealment was provided and pregnancy outcomes were followed up for 6 months post antioxidant treatment capturing both spontaneous conception and assisted reproductive technique-related pregnancies. Live birth occurred in 13% (17/131) of the antioxidant group compared with 5.3% (7/132) in the placebo group, with a statistically significant difference reported (p=0.031). Clinical pregnancy occurred in 19.8% (26/131) of the antioxidant group compared with 11.4% (15/132) in the placebo group, with a statistically significant difference reported (p=0.04).

Matthieu d'Argent 2021 randomised 162 men with at least one abnormal spermatic (WHO 2010 criteria) to receive folic acid (15 mg) daily or placebo for 3 months in a double-blind RCT. There were some concerns regarding overall risk of bias as no information on allocation sequence concealment was provided. The evidence was indirectly applicable since 20% of participants had mixed infertility. Clinical pregnancy was significantly higher (p=0.01) in the folic acid group 26/83 (35.6%) than the placebo 15/79 (20.4%). Miscarriage rates were higher (p=0.082) in the folic acid group 5/26 (19.2%) than the placebo 1/15 (6.7%).

Schisterman 2020 randomised 2370 men seeking infertility treatment to folic acid (5 mg) plus zinc (30 mg) or placebo for 6 months in a large, multicentre, double-blind RCT. This appears to be a high-quality study reporting concealed allocation and low risk of bias in all domains. Live birth was not significantly different

(Risk difference: −0.9% (95% CI: −4.7% to 2.8%) between the folic acid plus zinc group 404/1185 (34%) and the placebo group 416/1185 (35%). No significant difference (Risk difference: −1.0 (95% CI: −4.9 to 2.8) was observed in clinical pregnancy rates between the folic acid plus zinc group 449/1185 (38%) and the placebo group (462/1185 (36%).

Steiner 2019 recruited to the MOXI clinical trial 171 men with infertility ≥ 12 months, presence of at least one abnormal semen parameter in previous 6 months (such as DNA fragmentation ≥25%, oligospermia, asthenospermia, and teratospermia). Participants were randomised to either an antioxidant formulation group (containing 500 mg of vitamin C, 400 mg of vitamin E, 0.20 mg of selenium, 1,000 mg of l-carnitine, 20 mg of zinc, 1,000 µg of folic acid, 10 mg of lycopene daily) or a placebo group for 3 to 6 months. This appears to be a high-quality study reporting concealed allocation and low risk of bias in all domains. Live birth occurred in 15% (13/85) of couples in the antioxidant group compared with 24% (21/86) in the placebo group, with no significant difference observed (p=0.14). Clinical pregnancy was observed in 17.6% (15/85) of couples in the antioxidant group compared with 25.6% (22/86) in the placebo group, with no significant difference observed (p=0.11). Miscarriage rates were higher 22.2% (4/18) in the antioxidant group compared with 19.2% (5/26) in the placebo group, with no significant difference observed (p=1.0)

Stenqvist 2018 randomised 79 men with sperm DNA fragmentation (SCSA ≥25%) to antioxidant treatment with a commercial fertility supplement containing vitamins (vitamin C 30 mg, vitamin E 5 mg and vitamin B12 0.5 lg), antioxidants (l-carnitine 750 mg coenzyme Q10 10 mg and folic acid 100 lg) and oligoelements (zinc 5 mg and selenium 25 lg) with maltodextrin, calcium carbonate, citric acid, steviol glycoside, flavours, beta-carotene and silicon dioxide) vs control group receiving placebo (maltodextrin, calcium carbonate, citric acid, steviol glycoside, flavours, beta-carotene and silicon dioxide). The study had some concerns regarding outcome reporting due to the method used to confirm clinical pregnancy was not provided. Clinical pregnancy rates were 8.1% (3/37) in the antioxidant group versus 10% (4/40) in the placebo. The results were not statistically significant different and highlighted that antioxidant treatment in men with normal levels of reproductive hormones and high DFI found no significant improvement pregnancies.

Data pooled for antioxidants versus placebo showed no clear consistent evidence of benefit across outcomes. For live birth (3 studies: Lahimer 2023; Schisterman 2020; Steiner 2019), the pooled odds ratio was 1.05 (95% CI 0.19–5.97), indicating no clear effect. For clinical pregnancy (6 studies: Habibi 2022; Lahimer 2023; Matthieu d'Argent 2021; Schisterman 2020; Steiner 2019; Stenqvist 2018), there was a non-significant trend towards improved clinical pregnancy rates (OR 1.24, 95% CI 0.69–2.21). Miscarriage outcomes (2 studies: Matthieu d'Argent 2021; Steiner 2019) were highly imprecise with wide confidence intervals and substantial uncertainty in the effect estimate (OR 1.63, 95% CI 0.00–630.71).

Sperm Selection

Hasanen 2020 randomised 396 men with abnormal sperm DNA fragmentation (TUNEL ≥20.3%) to physiological intracytoplasmic sperm injection (PICSI) or magnetic-activated cell sorting (MACS) during intracytoplasmic sperm injection (ICSI). The overall risk of bias for this trial was low. There were no statistically significant differences in clinical pregnancy (p=0.89), occurring in 55.7% (111/200) of couples in the PICSI group compared with 56.4% (110/196) in the MACS group. Similarly, no statistically significant differences were observed in ongoing pregnancy (p=0.95), occurring in 62.4% (125/200) of couples in the PICSI group compared with 62.1% (122/196) in the MACS group. Subgroup analysis showed MACS was associated with a significantly higher ongoing pregnancy rate than PICSI in women under 30 years (69.5% vs 51.3%, p=0.015), while PICSI showed a trend towards higher pregnancy rates in women aged 30–35 years.

Hozyen 2022 randomised 223 men with sperm DNA fragmentation (TUNEL ≥20.3%) undergoing intracytoplasmic sperm injection (ICSI) to four sperm selection techniques: density gradient centrifugation (DGC) n = 72, testicular sperm retrieval (Testi) n = 73, physiological intracytoplasmic sperm injection (PICSI) n = 78, and magnetic-activated cell sorting (MACS) n =79. There were some concerns regarding overall

risk of bias as no information on allocation sequence concealment was provided. Clinical pregnancy was highest in the PICSI group (69.2%) compared with DGC (51.3%), with a significant difference reported (p=0.025). Ongoing pregnancy was also higher with PICSI (62.8%) and MACS (62.0%) compared with DGC (45.8%), with a significant difference observed between groups (p=0.003). Miscarriage rates were similar across all groups, with no significant differences reported.

Mantravadi 2024 randomised 150 men with sperm DNA fragmentation (SDF) ≥30% undergoing intracytoplasmic sperm injection, all of whom had either a prior failed in vitro fertilisation cycle or recurrent miscarriage. Participants were allocated to sperm selection using magnetic-activated cell sorting (MACS) or testicular sperm aspiration (TESA). This was an open-label trial with a low risk of bias. Live birth rates were similar between groups (41.3% vs 44% intention-to-treat), with higher rates per embryo transfer (63% vs 56%). Miscarriage rates were 5.3% and 11%, respectively, with no clear difference between approaches.

Data were not pooled for sperm selection because the studies were not sufficiently comparable in terms of interventions, comparators, or outcomes.

Ejaculatory Abstinence

Kabukcu 2021 randomised 120 couples with unexplained infertility undergoing intrauterine insemination to 1-day versus 3-day ejaculatory abstinence. The study was deemed to have a low risk of bias overall. Clinical pregnancy rates were not significantly different between groups, occurring in 17.3% with 1-day abstinence compared with 18.5% with 3-day abstinence (p=0.803). Overall, shortening ejaculatory abstinence did not significantly affect sperm DNA fragmentation or pregnancy outcomes in intrauterine insemination cycles.

Recommendation: GREY for all outcomes.

Justification: Evidence comes from 11 RCTs of highly variable quality with inconsistent results for all outcomes. Only one single large high-quality trial which shows no effect, while smaller trials report mixed findings with variable quality and limited precision. Overall, the evidence does not show a consistent benefit of antioxidants, sperm selection or ejaculatory abstinence. Miscarriage was often not defined, with follow-up not beyond the observation of clinical pregnancy.

1 (ii) *Female - recurrent miscarriage*

No studies were identified that included a population of female patients with recurrent miscarriage undergoing assisted reproduction.

Recommendation: GREY for all outcomes.

COMPARISON WITH PREVIOUS REVIEWS

A Cochrane systematic review by de Ligny 2022 evaluated the effectiveness and safety of supplementary oral antioxidants in subfertile men. The review reported on 90 studies (n = 10,303 men) which compared and combined 20 different oral antioxidants. Low-certainty evidence suggested that antioxidants were found to improve live birth (OR 1.43, 95% CI 1.07 to 1.91, P = 0.02, 12 RCTs, 1283 men, I2 = 44%, very low-certainty evidence) and clinical pregnancy rates may increase (OR 1.89, 95% CI 1.45 to 2.47, P < 0.00001, 20 RCTs, 1706 men, I2 = 3%, low-certainty evidence). There was no evidence of increased risk of miscarriage (OR 1.46, 95% CI 0.75 to 2.83, P = 0.27, 6 RCTs, 664 men, I2 = 35%, very low-certainty evidence). However, given the ‘low’ to ‘very-low’ certainty of the evidence, it was concluded that the current evidence base was inconclusive and further large well designed RCTs studying infertile men and reporting on pregnancy and live births were required to determine the exact role of antioxidants.

Recent guidelines published by The National Institute for Health and Care Excellence (NICE) on sperm DNA fragmentation (Guideline: NG257, published March 2026) found limited, low quality and inconsistent evidence to demonstrate the effectiveness of treating sperm DNA fragmentation. It reported high variability in sperm DNA fragmentation assays and thresholds for assessment of DNA damage from a very heterogeneous population. There was inconsistent evidence regarding the types, doses, and combinations of supplements, antioxidants (including post-varicocelectomy antioxidants), and medical treatments (such as offering surgical sperm retrieval), with no clear benefits of treating sperm DNA fragmentation, or justification for routine testing of sperm DNA fragmentation. It was recommended for further research to identify and validate the most appropriate assay and define a threshold for high DNA fragmentation, establish a link between elevated DNA fragmentation and subfertility, and develop a standardised antioxidant and vitamin treatment and dose.

DISCUSSION

Caution is required as the assessments above are made from a methodological perspective without expertise in the clinical or scientific context. It is worth noting that it is not uncommon for a trial to be well-designed to answer a question of little clinical value.

The recommendations for rating are intended only as a starting point for committee discussion.
Some comparisons contain a range of interventions (e.g. varied quantity, timing and duration of dose) in populations defined by different eligibility criteria. Alternative post-hoc but biologically plausible rationales could be put forward to ‘lump’ or further ‘split’ categories presented above.

REFERENCES: Reviewed studies

Adjunct	Study	DOI/reference
Sperm DNA fragmentation		
General population		
Male		
Antioxidant	Barekat, 2016	https://doi.org/10.22074/ijfs.2016.4777
	Habibi, 2022	https://doi.org/10.22074/cellj.2022.8273
	Lahimer, 2023	https://doi.org/10.3390/antiox12111937
	Matthieu d'Argent, 2021	https://doi.org/10.3390/jcm10091876
	Schisterman, 2020	https://dx.doi.org/10.1001/jama.2019.18714
	Steiner, 2019	https://doi.org/10.1016/j.fertnstert.2019.11.008
	Stenqvist, 2018	https://doi.org/10.1111/andr.12547
Sperm Selection	Hasanen, 2020	https://dx.doi.org/10.1007/s10815-020-01913-4
	Hozyen, 2022	https://doi.org/10.1007/s43032-021-00642-y
	Mantravadi, 2024	https://dx.doi.org/10.1007/s10815-024-03128-3
Ejaculatory Abstinence	Kabukcu, 2021	https://dx.doi.org/10.1007/s00404-020-05783-0
Other Reviews		
Cochrane review	de Ligny, 2022	https://dx.doi.org/10.1002/14651858.CD007411.pub5
NICE guideline	NICE (2026) NG257	https://www.nice.org.uk/guidance/ng257/evidence/s-sperm-dna-fragmentation-pdf-563921039736

Review of authorised use of In Vitro Maturation for oocytes

Details about this paper

Area(s) of strategy this paper relates to:	Supporting scientific and medical innovation
Meeting	Scientific and Clinical Advances Advisory Committee (SCAAC)
Agenda item	9
Paper number	HFEA (03/06/2026) 009
Meeting date	3 June 2026
Author	Mina Mincheva, Policy Manager
Annexes	Annex A – Clinical background of oocyte in vitro maturation (IVM) Annex B – Authorised processes decision tree

Output from this paper

For recommendation or decision?	For decision
Recommendation:	Members are asked to: • advise if the activity described in 2.3 falls under the scope of the existing authorised process 'In vitro maturation (for oocytes that are retrieved from antral or pre-ovulatory follicles)' • advise whether a new process application for the activity described in 2.3 is required.
Resource implications:	TBC
Implementation date:	Following SCAAC discussion
Communication(s):	As needed
Organisational risk:	Low

1. Introduction

1.1. As the UK regulator of fertility clinics, the HFEA maintains a list of authorised processes, which was first introduced in May 2011, that clinics can use to carry out the licensable activities set out in the Human Fertilisation and Embryology Act 1990 (as amended), (the HFE Act). If a centre wishes to carry out a process which does not appear on the list, it must apply to the Authority for permission. In March 2024, the Authority approved revisions to the authorised processes list and delegated the authorisation of new processes to the Scientific and Clinical Advances Advisory Committee (SCAAC) in March 2024.

1.2. SCAAC should consider a new process application as follows (see Annex B for authorised processes decision tree):

1.2.1. SCAAC should agree that the process is sufficiently different from any of the processes currently authorised to be considered as new.

1.2.2. The Committee should make a judgement on whether the evidence is sufficient to satisfy committee members that the process does not render the tissues or cells clinically ineffective or harmful to the recipient. In the event of the evidence not being fully conclusive, SCAAC members should use their judgement based on a compound level of risk and the strength of the evidence.

1.2.3. If approved, the SCAAC define the criteria for mandatory reporting including the data requirements (KPIs), timeframe and intervals for reporting. The HFEA Executive propose that SCAAC consider a standard 3-year initial period of mandatory reporting upon approval to ensure that the use of a new authorised process is reconsidered within a minimum timeframe. Depending on the perceived level of risk associated with the process or its anticipated frequency of use, the SCAAC may wish to reduce the timeframe for mandatory reporting to enable reconsidering a process at an earlier date.

1.2.4. If upon reconsideration of an authorised process, the evidence to support its ongoing use (arising from mandatory reporting requirements) is inconclusive, the SCAAC may:

a) reinstate/extend the requirement for mandatory enhanced reporting,
b) place additional conditions on the use of a process (eg restrict the process to a defined patient group),
c) monitor on a more regular basis through committee discussions, or
d) (in exceptional circumstances) suspend the process until a decision can be taken.

1.3. Regarding activities with a research purpose, the Licence Committee grants research licenses for activities specified in Paragraph 3 (1), (2) or (3), or Paragraph 2 (1) or (1A) of Schedule 2 in the HFE Act (as amended). Briefly summarised these are:

- bringing about the creation of embryos (or human admixed embryos) in vitro for the purposes of a project of research
- keeping or using embryos (or human admixed embryos) for the purposes of a project of research
- mixing sperm with the egg of a hamster, or other animal specified in directions, for the purpose of developing more effective techniques for determining the fertility or normality of sperm, but only where anything which forms is destroyed when the research is complete and, in any event, no later than the two cell stage

1.4. The research activities applied for are considered against the relevant licensable activities under Paragraph 1 (1) of Schedule 2 of the HFE Act (as amended). The Authority grants a research licence for one or more of the permitted research purposes defined in Paragraph 3A (1) and (2) of Schedule 2 in the HFE Act (as amended). Research licences are not required to conduct research on sperm or eggs.

1.5. The authorised processes list has been designed to encompass high-level processes, focusing on processes more broadly rather than on different methodologies used to perform them and the purpose(s) for which they may be used. This means that there may be several methodologies and purposes by which an authorised process can be undertaken, unless specified by the Authority. Fertility clinics that hold an HFEA licence are permitted to undertake the appropriate authorised process as part of their clinical practice, in accordance with the licence they hold.

1.6. The use of 'in vitro maturation (IVM) for oocytes that are retrieved from antral or pre-ovulatory follicles' is an HFEA authorised process on the authorised processes list under treatment licensed activity 'Processing gametes'.

1.6.1 It is being brought to the attention of SCAAC due to a recent enquiry from an HFEA licensed clinic wishing to develop and undertake IVM of immature oocytes recovered during ovarian tissue cryopreservation as a clinical service.

1.6.2 The discussion related to this enquiry will help clarify and detail the purpose of the authorised process 'IVM for oocytes that are retrieved from antral or pre-ovulatory follicles'

1.6.3 Therefore, the Executive does not bring this paper to SCAAC's consideration under the procedure for a new authorised process application described in 1.2., but to advise on whether the activity described in 2.3 falls under the existing authorisation of 'IVM for oocytes that are retrieved from antral or pre-ovulatory follicles.'

2. In vitro maturation – current status

2.1. In vitro maturation (IVM) – a method for supporting maturation of immature oocytes in vitro – is a blanket term applied to the process used to obtain mature oocytes from immature cumulus-oocyte complexes (COCs) retrieved from antral follicles. There are different methods of IVM, which typically involve some form of ovarian stimulation or gonadotropins and an in vitro maturation step. The most commonly used IVM methods are standard (or clinical) IVM and bi-phasic IVM (Gilchrist *et al.*, 2024). Another form of IVM is rescue IVM – maturation in vitro of cumulus denuded oocytes at germinal vesicle (GV) stage of development that have been needle aspirated in conventional IVF/ICSI cycles following controlled ovarian stimulation (Veeck *et al.*, 1983). Annex A provides further detail on clinical and bi-phasic IVM as well as respective patient groups for whom these procedures are used.

2.2. IVM was included on the authorised processes list in May 2011. The wording of this process did not change when the authorised processes list was revised in March 2024. In January 2026, after discussion with some SCAAC members, the wording of the process was updated from 'In vitro maturation' to 'In vitro maturation (for oocytes that are retrieved from antral or pre-ovulatory follicles)' to clarify that the permitted clinical purpose of this process refers to oocytes only. This includes both clinical scenarios, rescue IVM where immature oocytes have been recovered from pre-ovulatory follicles, and standard IVM – where immature oocytes (at GV or metaphase I stage)

have been needle aspirated from antral follicles of unstimulated ovaries and matured in vitro to metaphase II.

2.3. In December 2025, the Executive received an enquiry from a HFEA licensed clinic enquiring about performing IVM as a clinical service on fresh immature oocytes recovered from ovarian tissue of ovarian tissue cryopreservation (OTC) patients. Another patient group to whom this service would be offered is patients undergoing ovariectomy for other medical reasons (eg where the ovarian tissue itself is not suitable for cryopreservation for example, due to a risk of malignant contamination).

2.3.1. As first step, the clinic proposes to use surplus immature oocytes resulting from controlled ovarian stimulation to optimise an IVM protocol.

2.3.2. The clinic would then use the optimised protocol to undertake in vitro maturation of fresh oocytes recovered from the ovarian tissue of OTC patients. That would be followed by cryopreservation of these in vitro matured oocytes, or they would be used for in vitro fertilisation to create embryos for clinical treatment.

2.3.3. The oocytes identified are immature (GV or metaphase I stage) at the time of recovery. The immature oocytes retrieved during ovarian tissue cryopreservation are identified incidentally during routine cortical tissue processing and are not obtained from aspirated large antral follicles. Specifically, oocytes may be recovered from:

- small antral follicles present within the cortical tissue at the time of processing (typically <5 mm in diameter), or
- early antral or late pre-antral (secondary) follicles that become disrupted during mechanical preparation of cortical strips.

2.4. The enquiry about the above proposed activity under the authorised process 'IVM (for oocytes that are retrieved from antral or pre-ovulatory follicles)' is therefore brought to SCAAC for consideration in the context of using IVM on very immature oocytes aspirated from earlier stage follicles, or immature oocytes dissected from the ovarian tissue for clinical purpose.

3. Recommendations

3.1. Members are asked to:

- advise if the activity described in 2.3 falls under the scope of the existing authorised process 'In vitro maturation (for oocytes that are retrieved from antral or pre-ovulatory follicles)'
- advise whether a new process application for the activity described in 2.3 is required.

3.2. The Committee may wish to consider:

1) whether the procedure of retrieving eggs from ovarian tissue is any different to egg retrieval with standard needle aspiration in terms of risks;
2) the biological differences in maturation stage of oocytes retrieved via dissection from ovarian tissue vs oocytes retrieved by standard needle aspiration;
3) whether the in vitro maturation process of oocytes retrieved from ovarian tissue would present more risks to that of oocytes from needle aspiration in relation to their maturation stage at the start of the procedure and the resulting developmental competency.

4. References

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5. Annex A – Clinical background of oocyte in vitro maturation

5.1.

Standard/clinical IVM involves retrieval of immature germinal vesicle (GV) stage oocytes from small follicles (2–10 mm in diameter) and culture of intact cumulus-oocyte complexes (COCs) in vitro in one step until the metaphase II stage (MII) from unstimulated or FSH-primed patients (Edwards, 1965). Indications for standard/clinical IVM are patients with polycystic ovarian syndrome (PCOS), cancer patients for fertility preservation before chemotherapy and women who do not respond to gonadotropin stimulation (Gilchrist *et al.*, 2024; Lundin *et al.*, 2023). According to the ESHRE good practice recommendations on add-ons in reproductive medicine (Lundin *et al.*, 2023) the use of standard IVM for the indications mentioned above, is not considered an add-on. For any other indication, such as women with regular cycles and normal antral follicle count (AFC), the recommendations consider standard IVM to be an add-on. Though safer (no risk of ovarian hyperstimulation syndrome, OHSS) results from standard IVM are inferior to traditional IVF (Vuong *et al.*, 2020). Standard IVM is routinely used in Belgium at Brussels IVF fertility centre for patients with PCOS and some cancer patients.

5.2.

Bi-phasic IVM entails maturation in vitro of immature GV-stage intact cumulus-oocyte complexes (COCs) in two steps, from unstimulated or FSH-primed patients. Intact COCs are GV-arrested in step one (called pre-IVM) and matured in step two. In the pre-IVM phase, intact COCs are deliberately arrested at the GV stage, the purpose of which allow for cytoplasmic maturation of the oocyte (Gilchrist *et al.*, 2024). The current version of bi-phasic IVM, using a c-type natriuretic peptide (CNP)-mediated pre-IVM phase (called CAPA-IVM) has been introduced in human studies in 2020 and is still at experimental level (Gilchrist *et al.*, 2024).

5.3. To date, biphasic IVM has been reported in just three types of patients, including women diagnosed with PCOS, women with a high AFC, and women with gynaecological malignancies (Gilchrist *et al*., 2024).

5.4. Recent data on two and five-year follow-up of children born from CAPA-IVM vs IVF in patients with high AFC report no significant concerns regarding the effects of CAPA-IVM on developmental progress and emotional wellbeing of children (Vuong *et al.*, 2020, Vuong *et al.*, 2026).

5.5. Bi-phasic IVM is likely to become particularly important in future ART scenarios, such as in vitro follicle development and in vitro gametogenesis as it has the potential to endow developmental competence in vitro on oocytes that are otherwise developmentally incompetent.

6. Annex B – Authorised processes decision tree