# Scientific and Clinical Advances Advisory Committee (SCAAC) - agenda

## Monday 11 October 2021, 11:00am – 2:00pm
## Teleconference meeting via Zoom

| Agenda item | Time |
|---|---|
| 1. **Welcome, apologies, declarations of interest** | 11:00am (5') |
| 2. **Matters arising**<br>Victoria Askew (HFEA) | 11:05am (5') |
| 3. **Chair's business** | 11:10am (10') |
| 4. **SCAAC governance**<br>Julia Chain (HFEA Chair)/Peter Thompson (HFEA) | 11:20am (10') |
| 5. **Monitoring the effects of COVID on fertility, assisted conception and early pregnancy**<br>All | 11:30am (10') |
| 6. **Review of traffic light ratings for treatment add-ons**<br>Victoria Askew (HFEA), Andy Vail (The University of Manchester) | 11:40am (40') |
| *Lunch break* | *12:20pm (15')* |
| 7. **Review of traffic light ratings for treatment add-ons**<br>Victoria Askew (HFEA), Andy Vail (The University of Manchester) | 12:35pm (40') |
| 8. **Update on evolving the treatment add-ons information**<br>Clare Ettinghausen (HFEA)/Sonia Macleod (HFEA) | 1:15pm (10') |
| 9. **New technologies in embryo testing including PGT-M and PGT-A – literature review**<br>Sebastiaan Mastenbroek (University of Amsterdam) | 1:25pm (25') |
| 10. **Any other business** | 1:50pm (5') |
| 11. **Meeting summary and close** | 1:55pm (5') |

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

## Monday 11ᵗʰ October 2021

| Date and item | Action | Responsibility | Due date | Progress to date |
|---|---|---|---|---|
| 06/06/2020 | The Committee agreed to monitor research into the effects of COVID-19 on reproduction or early pregnancy and to discuss this research in a standing agenda item. | All SCAAC members | Ongoing | The Committee were reminded to highlight relevant papers ahead of the meeting. An agenda item will be scheduled at SCAAC meetings for this discussion. |
| 07/06/2021 | The Executive will amend the decision tree so that SCAAC have the option to recommend the addition of information for a green rated add-on to the HFEA website, rather than just red/amber. | Victoria Askew, Policy Manager | Ongoing | Updates to the treatment add-ons application form will be considered as part of the HFEA's work to review the traffic light rating system. |
| 07/06/2021 | A full review of the evidence, including biostatistical analysis from Andy Vail, will be conducted before ERA is considered again at the October meeting and a RAG rating is decided. | Victoria Askew, Policy Manager | Complete | Relevant published paper and comments from independent expert included as part of the paper for agenda items 6 and 7 of this meeting. |
| 07/06/2021 | The Executive to circulate guidelines for how to implement AI in medicine among SCAAC members. | Victoria Askew, Policy Manager | Ongoing | Although a member drew attention to publications during the meeting no papers or guidelines were sent to the executive by the Committee to circulate. The Executive requests that members forward any |

| | | | | relevant papers to the Executive for circulation. |
|---|---|---|---|---|
| 07/06/2021 | Intelligence team to consider the age brackets used in Fertility Trends report. | Victoria Askew, Policy Manager | Complete | The Intelligence team has been informed and will consider this when producing future reports. |

# Treatment add-on traffic light rating review – October 2021

## Details about this paper

| | |
|---|---|
| Area(s) of strategy this paper relates to: | The best care |
| Meeting: | Scientific and Clinical Advances Advisory Committee (SCAAC) |
| Agenda item: | 6 and 7 |
| Paper number: | HFEA (11/10/2021) 006 and 007 |
| Meeting date: | 11 October 2021 |
| Author: | Victoria Askew, Policy Manager |
| Annexes | Annex 1: Treatment add-ons traffic light ratings review<br>Annex 2: Independent reviewer report |

## Output from this paper

| | |
|---|---|
| For information or recommendation? | For recommendation |

| | |
|---|---|
| Recommendation: | The committee is asked to:<br><br>• consider the quality of evidence for each treatment add-on based on the findings from an independent assessor at annex A;<br><br>• agree and recommend traffic light categories for each treatment add-on based on the outcome of live birth rate;<br><br>• recommend information about outcomes other than live birth rate (time to pregnancy, miscarriage rates, risk of ovarian hyperstimulation syndrome etc) to be included on the HFEA website for each of the treatment add-ons<br><br>• recommend information about risks and safety to be included on the HFEA website for each of the treatment add-ons; and<br><br>• if a treatment add-on is given a green rating, recommend information for inclusion on the **'treatment options'** section of the HFEA website (if the add-on has been promoted from a red/amber rating to a green rating a link should be created from the main add-ons page for a period of time to raise awareness) |
| Resource implications: | In budget |
| Implementation date: | Recommendations will be considered by the HFEA for implementation in due course |
| Communication(s): | Communication of revised traffic light ratings if any change in a Clinic Focus and HFEA website update |
| Organisational risk: | Low |

# 1.    Introduction

**1.1.**    Treatment add-ons are optional additional treatments, offered on top of the main fertility treatment such as in vitro fertilisation (IVF), that claim to improve patients' chances of having a baby but the evidence to support this for most fertility patients is usually missing or not very reliable. They're sometimes emerging techniques that may have shown some promising results in initial studies, or they may have been around for a number of years but haven't necessarily been proven to improve live birth rates for most fertility patients.

**1.2.**    The HFEA has been concerned about the use of treatment add-ons for some years, and published a **consensus statement** co-signed by 10 leading professional and patient fertility groups, outlining agreed principles on how add-ons should be offered ethically in clinical practice in the UK.

**1.3.**    Since Spring 2017, the HFEA has published patient information on the treatment add-ons with limited evidence, each assigned with a traffic light rating agreed by the SCAAC reflecting the evidence in published randomised control trials (RCTs) of the effectiveness of the add-on (as measured by increasing a patient's chances of having a baby).

**1.4.**    The HFEA agreed that these were the treatment add-ons that patients most need information about, but this is not the complete list of additional treatments that patients may be offered on top of the main fertility treatment. The list of add-ons that the HFEA currently provides patient information on with a traffic light rating are:

- Artificial egg activation calcium ionophore
- Assisted hatching
- Elective freeze-all cycles
- Endometrial scratching
- Hyaluronate enriched medium (eg EmbryoGlue)
- Intracytoplasmic morphologic sperm injection (IMSI)
- Intrauterine culture
- Physiological intracytoplasmic sperm injection (PICSI)
- Pre-implantation genetic testing for aneuploidy (PGT-A)
- Immunological tests and treatments for fertility
- Time-lapse incubation and imaging

**1.5.**    In **June 2021**, the Committee considered and agreed an application to add Endometrial Receptivity Array (ERA) to the HFEA's traffic light rated list of add-ons. The traffic light rating for this treatment add-on will be agreed by the Committee in this meeting and patient information for ERA will be added the HFEA website in due course.

**1.6.**    Information is also provided for DNA fragmentation which may be offered to patients in several clinics. There is no traffic light rating for DNA fragmentation as after consulting with an andrology expert, SCAAC decided (at its **October 2018 meeting**) that this was

not feasible, as DNA fragmentation is a diagnostic test and does not directly influence live birth rate.

**1.7.**     HFEA work on treatment add-ons continues to develop over time. In February 2021 the HFEA **treatment add-ons webpage** was updated to make it clear that the traffic light ratings reflect the evidence base for most fertility patients. If there is evidence for benefit in specific subgroups or for outcomes other than live birth rate this is now outlined on the treatment add-ons individual page.

## 2.     Traffic light system

**3.**     Our traffic-light rated list of add-ons consists of three colours that indicate whether the evidence, in the form of high-quality RCTs, shows that a treatment add-on is effective at improving the chances of having a baby for someone undergoing fertility treatment. The traffic light ratings of the 11 treatment add-ons assessed so far are:

| Traffic light rating | Definition | Add-ons currently under this rating |
|---|---|---|
| 🔴 Red | No evidence from RCTs to show that it is effective at improving the chances of having a baby for most fertility patients | Assisted hatching<br>PGT-A<br>IMSI<br>PICSI<br>Intrauterine culture<br>Immunological tests and treatments for fertility |
| 🟠 Amber | There is conflicting evidence from RCTs to show that an add-on is effective at improving the chances of having a baby for most fertility patients. | Artificial egg activation calcium ionophore<br>Elective freeze all cycles<br>Hyaluronate enriched medium (e.g. EmbryoGlue)<br>Endometrial scratching<br>Time-lapse imaging |
| 🟢 Green | There is more than one high quality RCT which shows that the procedure is effective at improving the chances of having a baby for most fertility patients. | *n/a - These treatment add-ons may be routinely used in fertility treatments. Information about green rated add-ons, for example ICSI to treat male factor infertility, can be found elsewhere on the HFEA website.* |

**3.1.**     Since the February 2021 update, the traffic light ratings now only indicate the effectiveness of a treatment add-on at improving the chances of having a baby, and do not indicate safety of the add-ons. Specific **safety concerns** about a treatment add-on

are now included in the information on the webpage for that treatment add-on, under the dedicated section 'Is this treatment add-on safe?'. Patients are encouraged to discuss questions about the safety and risks of an add-on with their clinic.

**3.2.** The traffic light ratings now only indicate the effectiveness of a treatment add-on at improving the chances of having a baby (a live birth). Should the independent reviewer report that RCTs for treatment add-ons highlight **other significant outcomes in addition to live birth rate** (time to pregnancy, miscarriage rates etc) these will be considered by the Committee. The Committee will then determine if there is any additional information that should be given to patients on the HFEA website.

**3.3.** To account for new evidence that arises from RCTs conducted investigating treatment add-ons, the list of treatment add-ons and their assigned traffic light ratings are reviewed annually to determine whether the traffic light rating should change. Traffic light ratings could both be promoted to a higher rating (e.g. red to amber or amber to green) or demoted (e.g. amber to red).

## 4.      Independent assessment of the quality of evidence

**4.1.** In order to categorise the treatment add-ons under consideration, it is necessary not only to identify the published evidence around 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[1]) for each treatment add-on.

**4.2.** The independent reviewer reassessed the traffic light ratings in light of the additional studies published since the last review (conducted in **October 2020**).  New research (the published evidenced) in the form of RCTs were identified for six of the 12 add-ons on the HFEA's traffic light rated list of add-ons. This includes ERA for which the Executive did a literature review for RCTs published over the last 10 years..

**4.3.** 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.

**4.4.** The findings of this assessment for each add-on and the independent reviewer's recommended ratings can be found at Annex A, alongside the current traffic light rating agreed previously in consultation with the committee, last in October 2020. The assessments made by the independent reviewer are from a methodological perspective without expertise in the clinical or scientific context.

**4.5.** The independent reviewer's original report can be found at Annex B.

## 5.      Recommendations

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[1] 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.

**5.1.**    The committee is asked to:

- consider the quality of evidence for each treatment add-on based on the findings from an independent assessor at annex A;

- agree and recommend traffic light categories for each treatment add-on based on the outcome of live birth rate;

- recommend information about outcomes other than live birth rate (time to pregnancy, miscarriage rates, risk of ovarian hyperstimulation syndrome etc) to be included on the HFEA website for each of the treatment add-ons;

- recommend information about risks and safety to be included on the HFEA website for each of the treatment add-ons; and

- if a treatment add-on is given a green rating, recommend information for inclusion on the **'treatment options'** section of the HFEA website (if the add-on has been promoted from a red/amber rating to a green rating a link should be created from the main add-ons page for a period of time to raise awareness)

## Annex A: Treatment add-ons traffic light ratings review

## 1.    Artificial egg activation calcium ionophore

| Current traffic light category | | Traffic light category recommended by independent reviewer – October 2021 |
|---|---|---|
| Amber | There is conflicting evidence from RCTs to show that an add-on is effective at improving the chances of having a baby for most fertility patients. | No new studies were reviewed as part of October 2021 review |

**1.1.**    Artificial egg activation calcium ionophore was introduced to the HFEA's traffic light rated list of add-ons in February 2017 and was assigned an amber traffic light rating by the Committee. No changes have been made to this traffic light rating since then.

**1.2.**    No RCTs for this treatment add-on were identified that had been published since the last review in October 2020. For this reason, no summary has been provided by the independent reviewer for this meeting.

## 2.    Assisted hatching

| Current traffic light category | | Traffic light category recommended by independent reviewer – October 2021 |
|---|---|---|
| Red | No evidence from RCTs to show that it is effective at improving the chances of having a baby for most fertility patients | No new studies were reviewed as part of October 2021 review |

**2.1.**    Assisted hatching was introduced to the HFEA's traffic light rated list of add-ons in February 2017 and was assigned a red traffic light rating by the Committee. No changes have been made to this traffic light rating since then.

**2.2.**    No RCTs for this treatment add-on were identified that had been published since the last review in October 2020. For this reason, no summary has been provided by the independent reviewer for this meeting.

## 3.    Elective freeze all cycles

| Current traffic light category | Traffic light category recommended by independent reviewer – October 2021 |
|---|---|
| ● Amber — There is conflicting evidence from RCTs to show that an add-on is effective at improving the chances of having a baby for most fertility patients. | ● Amber — There is conflicting evidence from RCTs to show that an add-on is effective at improving the chances of having a baby for most fertility patients. |

**3.1.**    Elective freeze all cycles was introduced to the HFEA's traffic light rated list of add-ons in February 2017 and was assigned an amber traffic light rating by the Committee. No changes have been made to this traffic light rating since then.

**3.2.**    The committee is asked to consider whether the HFEA website should increase messaging around the reduction of risk for ovarian hyperstimulation syndrome (OHSS) when undergoing freeze all cycles in light of the summary provided by the independent reviewer in points 3.3 – 3.6.

**Independent reviewer comments:**

**3.3.**    *The previous review in 2020 considered eight studies with the four most recent, published since 2018, all of strong methodological quality. Shi 2018, Vuong 2018 and Wei 2019 randomised after embryo development, whereas Stormlund 2020 randomised earlier to allow different triggering of final oocyte maturation and reduce risk of OHSS. Only Wei 2019 suggested strong benefit and this result appeared anomalous in the context. Only Vuong considered cumulative live birth, reporting similar success rates in terms of ongoing pregnancy out to 12 months.*

**3.4.**    *This review incorporates three new studies. Santos-Ribeiro 2020, like Stormlund 2020, randomised early to allow different treatment from the time of trigger. Studying just those at high risk of OHSS (≥18 follicles of ≥11mm) they found very similar live birth [OR (95% CI) = 1.1 (0.61 to 1.8)] and cumulative live birth results [OR (95% CI) = 0.95 (0.54 to 1.7)]. Importantly, they also reported successful elimination of moderate-to-severe OHSS: 0 vs 9 (9%). Stormlund 2020 similarly reported elimination of OHSS under the freeze-all strategy.*

**3.5.**    *Simón 2021 was intended as a study of ERA (see details below) but the two comparison groups provide a comparison of elective freeze-all with fresh transfer in low risk women scheduled for blastocyst transfer. Success rates were non-significantly lower in the frozen transfer group: live birth OR (95% CI) = 0.71 (0.45 to 1.1) and cumulative birth: OR=0.95 (0.61 to 1.5)]. Miscarriage was non-significantly higher (11 vs 5). Interpretation of this study is complicated however by the very large proportion of protocol deviations (see details under ERA below).*

**3.6.**    *Wong 2021 considered women with any indication, regardless of available numbers of follicles or embryos, undergoing their first treatment cycle. They randomised before the start of down-regulation and compared a policy of cryopreservation of all embryos on day 6 with a strategy of fresh single blastocyst transfer on day 5 followed by cryopreservation of all surplus embryos on day 6. Live birth rate following the first transfer was significantly lower in the freeze-all group - OR (95% CI) = 0.27 (0.11 to 0.66) – with correspondingly lower rates of clinical and ongoing*

*pregnancy. Cumulative rates to 12 months were also significantly lower for their primary outcome of ongoing pregnancy and lower also for cumulative live birth: OR (95% CI) = 0.54 (0.28 to 1.1).  Like Santos-Ribeiro 2020, there were no cases of OHSS in the freeze-all group: 0 vs 3 (3%) requiring hospitalisation.*

## 3.7.    **Recommendation: Amber**

# 4.    Endometrial receptivity array (ERA)

| Current traffic light category | Traffic light category recommended by independent reviewer – October 2021 | |
|---|---|---|
| N/A | Amber | There is conflicting evidence from RCTs to show that an add-on is effective at improving the chances of having a baby for most fertility patients. |

**4.1.**    Elective freeze all cycles was introduced to the HFEA's traffic light rated list of add-ons in June 2021 and is yet to be assigned a traffic light rating by the Committee.

**4.2.**    The executive preformed a literature review for RCTs published over the last 10 years investigating the effectiveness of ERA at increasing live birth rate, and other outcomes.

### Independent reviewer comments:

**4.3.**    *Just one study was identified for this assessment. Simón 2021 studied women under 37 years old with BMI 18.5 to 30 kg/m$^2$ who were scheduled for blastocyst transfer and had not suffered previous recurrent implantation failure or miscarriages.  They conducted a comparison of 'personalised embryo transfer' based on ERA with two different control groups – elective frozen ET and fresh ET.*

**4.4.**    *Although this was a moderately sized (n=458), multi-centre study its interpretation is compromised by early randomisation.  More than 10% of randomised participants did not proceed to embryo transfer, and over 40% did not receive the allocated intervention.*

**4.5.**    *For live birth after the first transfer, OR=1.3 (0.79 to 2.0) versus frozen and OR=0.90 (0.57 to 1.4) versus fresh transfer.  For cumulative live birth to 12 months these became OR=1.3 (0.82 to 2.0) and OR=1.2 (0.78 to 1.9) respectively.*

**4.6.**    *The paper reported 'per protocol' analyses that were slightly more favourable to the ERA group in each comparison.  It is perhaps also worth noting that miscarriage of clinical pregnancy was most common in the ERA group: 17 (ERA) versus 11 (frozen) versus 5 (fresh).*

**4.7.**    *Recommendation: Amber*

# 5.   Endometrial scratching

| Current traffic light category | Traffic light category recommended by independent reviewer - October 2021 | |
|---|---|---|
| | **Endometrial scratching (no-plausible biological mechanism for differences due to timing of scratch)** | |
| 🟠 Amber — There is conflicting evidence from RCTs to show that an add-on is effective at improving the chances of having a baby for most fertility patients. | 🟠 Amber — There is conflicting evidence from RCTs to show that an add-on is effective at improving the chances of having a baby for most fertility patients. | |
| | **Endometrial scratching timed during luteal phase of preceding cycle** | **Endometrial scratching not timed during luteal phase of preceding cycle** |
| | 🟢 Green — There is more than one high quality RCT which shows that the procedure is effective at improving the chances of having a baby for most fertility patients. | 🟠 Amber — There is conflicting evidence from RCTs to show that an add-on is effective at improving the chances of having a baby for most fertility patients. |

5.1.   Endometrial scratching was introduced to the HFEA's traffic light rated list of add-ons in February 2017 and was assigned an amber traffic light rating by the Committee. No changes have been made to this traffic light rating since then.

5.2.   The Committee is asked to consider whether there is a biologically plausible mechanism by which the timing of the endometrial scratching would justify the recommendation by the independent reviewer (detailed in points 5.4 to 5.21) of splitting the traffic light rating as outlined in the table above.

5.3.   If the Committee decides to split endometrial scratching into two separate traffic light ratings, the executive asks that the Committee give a recommendation of the appropriate title for the two scratch timings.

5.4.   The Committee is also asked to consider whether any information around safety considerations should be added to the HFEA website in light of the independent reviewer's comments in point 5.14.

**Independent reviewer comments:**

5.5.   *The previous review included 21 studies reporting on more than 4000 participants as well as two further studies randomising a further 2000 participants from the Netherlands (van Hoogenhuijze) and UK (Metwally) that were pre-publication.*

**5.6.**    *Studies of women undergoing IUI or natural cycles were of generally poor quality but surprisingly consistent in estimating clinical benefit of scratching.*

**5.7.**    *Studies of women undergoing IVF or ICSI cycles were less optimistic. The more recent, larger and higher quality studies suggested a small but non-statistically significant benefit of up to around 6 percentage points.*

**5.8.**    *This review considers the full published data of van Hoogenhuijze and Metwally and four additional trials.*

**5.9.**    *Peer reviewed results for van Hoogenhuijze 2021 and Metwally 2021 confirmed those included in the previous review.  In brief, both conducted the scratch procedure in the mid-luteal phase of the cycle preceding planned first (Metwally) or second (van Hoogenhuijze) cycle of IVF/ICSI in women of good prognosis.  Both were methodologically strong and reported higher success in the treatment arm that did not reach statistical significance.  Metwally reported that one participant of 449 who underwent the procedure did not find it "tolerable". In van Hoogenhuijze, 54% reported symptoms of blood loss, pain or fever with 12 considered "severe" and no hospitalisations.*

**5.10.**    *Ghuman 2020 and Yavangi 2021 both undertook small trials (n=75 per treatment) in women undergoing IUI.  Endometrial scratch was performed on days 6 to 7 of up to three cycles by Ghuman 2020 and on days 19 to 21 of a single cycle by Yavangi 2021. Neither study reported on live birth.  Ghuman 2020 reported cumulative ongoing pregnancy rate: OR (95% CI) = 0.73 (0.24 to 2.2).  Yavangi 2021 reported clinical pregnancy rate: OR (95% CI) = 1.3 (0.58 to 2.8). Ghuman reported pain scores with a mean of 7 out of 10 during the first cycle of treatment and correspondingly reduced adherence in subsequent cycles.*

**5.11.**    *Berntsen 2020 evaluated endometrial scratch injury during the follicular phase of the cycle preceding a second or subsequent intended cycle of IVF/ICSI. Unfortunately they describe a catalogue of errors in the design, conduct and analysis of their study.  These include erroneous sample size calculation, failing to recruit and running out of funding after extending the study, loss of all follow-up from a site that closed, and differential post-randomisation exclusions combined with a per-protocol approach to analysis. The live birth OR (95%CI) =1.4 (0.67 to 3.0) adds little to the evidence base.*

**5.12.**    *Rodriguez 2020 evaluated endometrial scratch injury during the luteal phase of the cycle preceding an intended fresh cycle of IVF/ICSI using donor oocytes. They reported slightly increased live birth rates: OR (95% CI) = 1.3 (0.85 to 2.0).  There was no reporting of tolerability.*

**5.13.**    *The addition of two further small studies of endometrial scratch during IUI cycles changes little from the previous review. Although both were less positive than previous results in this population they were relatively small studies given the totality of evidence.*

**5.14.**    *The addition of Rodriguez 2020 to the meta-analysis of live birth rates reported by recent, methodologically sound trials contributes 11% of this restricted evidence base and is sufficient to tighten the confidence interval around a small positive effect. Consistent results across the five studies (I2=0%) gives OR (95% CI) = 1.15 (1.00 to 1.32). This suggests, for example, that in a population of women undergoing IVF/ICSI with 35% chance of live birth, endometrial scratch could increase this to between 35% and 41%.*

**5.15.**    *The only one of these studies not to find a (statistically non-significant) benefit was Lensen 2019. Timing of the procedure in this study was left to clinician preference and not recorded, whereas other studies all performed the procedure during the luteal phase of the preceding cycle.  The Committee should consider whether timing is an important factor and note that Lensen 2019 was also the largest study, contributing 31% of the evidence. Omission of this study would marginally strengthen the case: OR (95% CI) = 1.22 (1.03 to 1.45).*

**5.16.** *It should also be noted that recent studies have reported pain, blood loss and fever associated with the procedure, although not to an extent resulting in hospitalisation.*

**5.17.** *The committee should consider whether it is biologically plausible that this add-on may affect implantation differentially between IVF/ICSI, where endometrial scratch is typically performed in the preceding cycle, and IUI/natural cycles, where it is usually performed in the index cycle. If so, then consideration could be given to providing separate ratings for the two clinical populations.*

**5.18.** ***Recommendation: Amber/Green (consistent evidence from multiple, well-designed trials that attains borderline statistical significance but with clear, associated adverse events.)***

**Further comments from independent reviewer:**

**5.19.** The executive requested further clarification from the independent reviewer regarding the recommendation of two traffic light ratings for endometrial scratching, included below:

**5.20.** *If timing of intervention within IVF/ICSI cycles is considered important, then there is sufficient evidence to recommend a green light for endometrial scratch taking place in the luteal phase of the preceding cycle. There is high quality and consistent evidence of a small effect.*

**5.21.** *If timing is less important, then the high quality, consistent evidence remains for IVF/ICSI cycles but is slightly weaker.*

**5.22.** *If the biological rationale for any effect is considered to be just as credible regardless of whether embryo transfer processes are involved, then the committee needs to weigh in the additional evidence, most of which they have seen previously, for natural/IUI treatment cycles. This is on the whole favourable too, so they may feel inclined to give an overall green light despite the inconsistency and low quality of this evidence.*

## 6.  Hyaluronate enriched medium (eg EmbryoGlue)

| Current traffic light category | | Traffic light category recommended by independent reviewer – October 2021 | |
| --- | --- | --- | --- |
|  Amber | There is conflicting evidence from RCTs to show that an add-on is effective at improving the chances of having a baby for most fertility patients. |  Amber | There is conflicting evidence from RCTs to show that an add-on is effective at improving the chances of having a baby for most fertility patients. |

**6.1.** Hyaluronate enriched medium was introduced to the HFEA's traffic light rated list of add-ons in February 2017 and was assigned an amber traffic light rating by the Committee. No changes have been made to this traffic light rating since then.

**6.2.** Of note, the Executive is aware that a randomised control trail is due to be published on Hyaluronate enriched medium. Depending on the outcome of this study there may be a need to re-review this traffic light rating before the next annual review period.

**Independent reviewer comments:**

**6.3.**    *The previous review in 2019 covered ten studies, including eight fully reported RCT with a total of over 2600 participants. The overall quality of studies was low with most at high risk of bias. The largest and methodologically strongest study, Urman 2008, included over 1200 participants and found significantly increased live birth rate with use of embryo glue.*

**6.4.**    *This review considers the additional evidence from Yung 2021. This is a well-conducted and clearly reported trial randomising 550 couples in Hong Kong planning frozen embryo transfer following an unsuccessful or cancelled fresh transfer cycle.  Reported live birth events were almost identical in the two groups: OR=0.98 (0.67 to 1.4) with very similar pregnancy losses, twin rates and obstetric outcomes.  Mean birthweight was approximately 200g more in the group allocated to embryo glue (3058g vs 2842g).*

**6.5.**    ***Recommendation: Amber***

# 7.    Intracytoplasmic morphologic sperm injection (IMSI)

| **Current traffic light category** | **Traffic light category recommended by independent reviewer – October 2021** |
|---|---|
| 🔴 Red — No evidence from RCTs to show that it is effective at improving the chances of having a baby for most fertility patients | No new studies were reviewed as part of October 2021 review |

**7.1.**    IMSI was introduced to the HFEA's traffic light rated list of add-ons in October 2018 and was assigned a red traffic light rating by the Committee. No changes have been made to this traffic light rating since then.

**7.2.**    No RCTs for this treatment add-on were identified that had been published since the last review in October 2020. For this reason, no summary has been provided by the independent reviewer for this meeting.

# 8.    Intrauterine culture

| **Current traffic light category** | **Traffic light category recommended by independent reviewer – October 2021** |
|---|---|
| 🔴 Red — No evidence from RCTs to show that it is effective at improving the chances of having a baby for most fertility patients | No new studies were reviewed as part of October 2021 review |

**8.1.**    Intrauterine culture was introduced to the HFEA's traffic light rated list of add-ons in February 2017 and was assigned a red traffic light rating by the Committee. No changes have been made to this traffic light rating since then.

**8.2.**     No RCTs for this treatment add-on were identified that had been published since the last review in October 2020. For this reason, no summary has been provided by the independent reviewer for this meeting.

## 9.  Physiological intracytoplasmic sperm injection (PICSI)

| Current traffic light category | | Traffic light category recommended by independent reviewer – October 2021 |
|---|---|---|
| 🔴 Red | No evidence from RCTs to show that it is effective at improving the chances of having a baby for most fertility patients | No new studies were reviewed as part of October 2021 review |

**9.1.**     PICSI was introduced to the HFEA's traffic light rated list of add-ons as in October 2018 and was assigned a red traffic light rating by the Committee. No changes have been made to this traffic light rating since then.

**9.2.**     No RCTs for this treatment add-on were identified that had been published since the last review in October 2020. For this reason, no summary has been provided by the independent reviewer for this meeting.

## 10.  Pre-implantation genetic testing for aneuploidy (PGT-A)

| Current traffic light category | | Traffic light category recommended by independent reviewer – October 2021 |
|---|---|---|
| 🔴 Red | No evidence from RCTs to show that it is effective at improving the chances of having a baby for most fertility patients | No new studies were reviewed as part of October 2021 review |

**10.1.**   PGT-A for day 5 embryos was introduced to the HFEA's traffic light rated list of add-ons in February 2017 and was assigned an amber traffic light rating by the Committee, this rating was changed to a red traffic light by the Committee in October 2019.

**10.2.**   No RCTs for this treatment add-on were identified that had been published since the last review in October 2020. For this reason, no summary has been provided by the independent reviewer for this meeting.

## 11. Immunological test and treatments for infertility

| Current traffic light category | | Traffic light category recommended by independent reviewer – October 2021 | |
|---|---|---|---|
| **Immunological test and treatments for infertility** | | **Steroids** | |
| 🔴 Red | No evidence from RCTs to show that it is effective at improving the chances of having a baby for most fertility patients | 🟠 Amber | There is conflicting evidence from RCTs to show that an add-on is effective at improving the chances of having a baby for most fertility patients. |
| | | **Intravenous immunoglobulins** | |
| | | 🔴 Red | No evidence from RCTs to show that it is effective at improving the chances of having a baby for most fertility patients |
| | | **Intralipids** | |
| | | 🟠 Amber | There is conflicting evidence from RCTs to show that an add-on is effective at improving the chances of having a baby for most fertility patients. |

**11.1.** Immunological test and treatments for infertility was introduced to the HFEA's traffic light rated list of add-ons as an umbrella term covering all immunological test and treatments for infertility treatments in February 2017 and was assigned a red traffic light rating by the Committee. No changes have been made to this traffic light rating since then.

**11.2.** At the **October 2020** SCAAC meeting it was proposed that immunological test and treatments for infertility be broken down by treatment type and an individual traffic light rating be allocated to each type. The Committee agreed that the title 'Reproductive Immunology' was confusing for patients and as an umbrella term is unhelpful. They recommended that the uses of steroids should be separated and that immunological tests should be separated from the immunological treatments. There is little scientific evidence for the tests or for a causal link between abnormal test results, recurrent implantation failure and the treatments given for it. The Committee were not happy to give separate traffic light ratings at this stage for steroids, IVIg and intralipids as they felt that the HFEA's information on immunological test and treatments for infertility needed to be made clearer first.

**11.3.** The Executive has since updated the information available to patients on the HFEA website, in consultation with SCAAC members and an external expert, now with the heading 'Immunological tests and treatments for fertility'. No new studies for immunological test and

treatments for infertility were identified since October 2020. Therefore, the results of the review from October 2020 are presented to the committee below.

**11.4.** It should be noted that no publications investigation TNF-a blocking agents were identified for inclusion in this review and therefore a traffic light rating has not been recommended.

**Independent reviewer comments:**

**Steroids**

**11.5.** *The nine studies of steroids considered quite different populations depending on the proposed mechanism of action.*

**11.6.** *Wiser 2010 studied a small number of women with a poor response to stimulation in a previous cycle of treatment. They found a marked increase in live birth rates for women given 75 mg oral dehydroepiandrosterone (DHEA) daily for a number of weeks prior to starting stimulation. The study was unblinded with unclear allocation concealment. Kara 2014 similarly gave DHEA to 200 women with diminished ovarian reserve in an unblinded study. They recorded almost identical clinical pregnancy rate between groups. Narkwichean 2017 undertook a feasibility and proof of concept study in 60 women undergoing their first IVF/ICSI cycle and with predicted diminished ovarian reserve. This study also used DHEA but incorporated matching placebo in a seemingly well designed and conducted trial. They observed slightly higher success amongst the control group.*

**11.7.** *Fawzy 2013 studied over 300 women with previous unexplained implantation failures. The intervention consisted of oral prednisolone 20 mg/day from the day of stimulation with 1mg/kg/day subcutaneous low molecular weight heparin (LMWH) from the day after oocyte retrieval until the day of pregnancy test (if negative) or week 8 of pregnancy. The authors reported a large increase in ongoing pregnancy but this study was unblinded and, more importantly, used entirely predictable alternation rather than randomisation to allocate participants. Results are therefore unreliable. Tartagni randomised 100 women with repeated IUI failures but normal ovarian reserve. They undertook a placebo-controlled trial of 75 mg oral DHEA daily for eight weeks prior to starting ovulation induction. They reported a higher live birth rate in the active group, most of which could be ascribed to more miscarriages in the control group.*

**11.8.** *The remaining four studies each targeted particular groups with different aims. Fan 2016 studied 130 women with antinuclear antibody who had experienced a previous implantation failure. Treatment consisted of prednisolone 10mg daily plus aspirin 100mg daily from 3 months before ovulation induction until clinical pregnancy. The trial was unblinded and unclear regarding allocation concealment. A large difference in clinical pregnancy was reported.*

**11.9.** *Taiyeb 2017 studied 240 men with anti-sperm antibodies. Treatment consisted of following a course of tapering prednisolone repeated in each of three menstrual cycles prior to IVF/ICSI. There was risk of bias from both unclear allocation concealment and blinding processes and methodological issues with post-randomisation exclusions. Reconstruction of an intention to treat comparison suggested a small and non-statistically significant advantage of treatment on clinical pregnancy rate.*

**11.10.** *Yeganeh 2017 studied over 200 women with PCOS with the aim of reducing the risk of OHSS. Intervention consisted of methylprednisolone: 1g intravenous on the days of oocyte retrieval and embryo transfer plus 16mg oral daily from the first day of stimulation through to pregnancy testing. This was another unblinded study at high risk of bias regarding allocation concealment but reported very similar clinical pregnancy rate in each group.*

**11.11.** *Most recently, Liu 2018 undertook a study of 450 women undergoing their first IVF cycle with no history of recurrent miscarriage who experienced raised progesterone levels on the third or fourth day of gonadotrophin stimulation. They compared 0.75mg daily oral dexamethasone with no treatment in another unblinded study.  They reported very similar outcomes in the fresh transfer cycle.  Follow-up for two years of all frozen transfers suggested an advantage of intervention for the outcome of cumulative live birth.*

**11.12.** *Recommendation: Amber, or red for most if separating populations*

### Intravenous immunoglobulins (IVIG)

**11.13.** *Two studies were reviewed.  Stephenson 2010 randomised 77 participants with idiopathic secondary recurrent miscarriage in a double-blind, placebo controlled trial. IVIG was delivered at a dose of 500mg/kg two to three weeks before the next anticipated menstrual period and then every four weeks for up to 6 cycles or until reaching 18 to 20 weeks gestation.  The size of study ruled out very little: live birth odds ratio (95% CI) was 1.2 (0.47 to 2.9); consistent with the intervention more than doubling or halving the odds of success.*

**11.14.** *Christiansen 2014 conducted a study of similar size in a similar patient population.  The main difference was that IVIG was first given on confirmation of pregnancy by repeated biochemical testing.  A total of eight infusions were given up to week 15 of gestation at a dose of approximately 25g for those up to 75kg of weight and 35g for heavier women.  Results were also very similar with live birth odds ratio (95% CI) of 1.2 (0.51 to 2.9).*

**11.15.** **Recommendation: Red**

### Intralipids

**11.16.** *This review included three studies.  Dakhly 2016 randomised nearly 300 participants with secondary recurrent miscarriage who were undergoing IVF to IV infusion on the day of oocyte retrieval or matching placebo. Unfortunately this was a poorly reported study with scope for serious bias in the allocation and blinding processes.  It was conducted with a policy of transferring two or three embryos.  The reported result was a marked increase in live birth rate with intervention: OR (95% CI) = 2.1 (1.3 to 3.5).*

**11.17.** *Singh 2019 studied about 100 women with recurrent implantation failure undergoing IVF. Infusions were given immediately following oocyte retrieval and again one hour after embryo transfer.  This too was a poorly reported study at risk of bias from both allocation concealment and blinding. It was also conducted with a policy of transferring two or three embryos when available. The reported result was a marked increase in live birth rate with intervention: OR (95% CI) = 3.3 (1.2 to 8.8).*

**11.18.** Al-Zebeidi 2019 studied nearly 150 women with unexplained recurrent implantation failure undergoing ICSI.  Infusions in this study were given at the time of embryo transfer and again at the time of pregnancy testing.  This too was a poor study at risk of bias from allocation concealment and with no attempt at blinding. A double embryo transfer policy was used with three embryos allowed for older women. Again the reported live birth result favoured intervention but this time without reaching statistical significance: OR (95% CI) = 1.4 (0.57 to 3.4).

**11.19.** *Recommendation: Amber*

## 12. Time-lapse imaging and incubation

| Current traffic light category | | Traffic light category recommended by independent reviewer – October 2021 | |
|---|---|---|---|
| Amber | There is conflicting evidence from RCTs to show that an add-on is effective at improving the chances of having a baby for most fertility patients. | Amber | There is conflicting evidence from RCTs to show that an add-on is effective at improving the chances of having a baby for most fertility patients. |

**12.1.** Time-lapse incubation and imaging was introduced to the HFEA's traffic light rated list of add-ons in February 2017 and was assigned a red traffic light rating by the Committee. No changes have been made to this traffic light rating since then.

### Independent reviewer comments:

**12.2.** *Time lapse incubation involves two distinct processes both hypothesised to deliver clinical benefits.  First, the ability to leave the embryo undisturbed during repeated assessment may be beneficial to the development process.  Independently, the additional information available through time-lapse imaging may bring benefits for embryo selection. Clinical trials reviewed previously fell into three broad categories evaluating effects of:*

- *i) the environment for embryo development (1 safety study without clinical implications);*
- *ii) the embryo selection process (2 studies at high risk of bias reported statistically non-significant benefits); and*
- *iii) the combined effect of the two (4 studies at high risk of bias with contrasting results).*

**12.3.** *This update identified a protocol published by Chen 2020 addressing effect (i) above.  This study is still in recruitment but plans to randomise 730 women with diminished ovarian reserve who are undergoing their first or second cycle of treatment. The protocol appears of high quality.  Correspondence with authors confirms that recruitment has been delayed but is currently ongoing with 201 participants randomised to date.*

**12.4.** *Recommendation: Amber*

# Annex B: Independent reviewer report

**Traffic Light System for Treatment Add-ons**

**Prof Andy Vail, October 2021**

INTRODUCTION

The HFEA website provides patients with digestible information on treatment add-ons in the form of a 'traffic light' system.  The purpose of this report is to inform the Scientific and Clinical Advances Advisory Committee's deliberations on updating this information.  In particular, further recent publications have been identified to supplement current reviews of four add-ons: elective freeze all; embryo glue; endometrial scratch and time-lapse incubation. A trial has also been identified to include a new review of endometrial receptivity array (ERA).

The aim of the work reported below was to critically appraise, interpret and summarise, for consideration by the HFEA, the reports of these studies.

METHOD

Victoria Askew, Policy Manager, provided references and hyperlinks to identified studies for consideration.  All papers were published in 2020 or 2021.

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.  Where it appeared overly simplistic to categorise all studies of a specific add-on together, results have been stratified in the results presented below.

To calculate odds ratios, published results were re-calculated applying the intention to treat (ITT) principle 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.  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, particularly those relating to safety such as OHSS incidence and miscarriage, are reported where these are a particular aim of the add-on.

RESULTS

**Updates to existing reviews**

*1. Elective freeze all*

The previous review in 2020 considered eight studies with the four most recent, published since 2018, all of strong methodological quality. Shi 2018, Vuong 2018 and Wei 2019 randomised after embryo development, whereas Stormlund 2020 randomised earlier to allow different triggering of final oocyte maturation and reduce risk of OHSS.  Only Wei 2019 suggested strong benefit and this result appeared anomalous in the context.  Only Vuong considered cumulative live birth, reporting similar success rates in terms of ongoing pregnancy out to 12 months.

This review incorporates three new studies.  Santos-Ribeiro 2020, like Stormlund 2020, randomised early to allow different treatment from the time of trigger.  Studying just those at high risk of OHSS (≥18 follicles of ≥11mm) they found very similar live birth [OR (95% CI) = 1.1 (0.61 to 1.8)] and cumulative live birth

results [OR (95% CI) = 0.95 (0.54 to 1.7)]. Importantly, they also reported successful elimination of moderate-to-severe OHSS: 0 vs 9 (9%).  Stormlund 2020 similarly reported elimination of OHSS under the freeze-all strategy.

Simón 2021 was intended as a study of ERA (see details below) but the two comparison groups provide a comparison of elective freeze-all with fresh transfer in low risk women scheduled for blastocyst transfer. Success rates were non-significantly lower in the frozen transfer group: live birth OR (95% CI) = 0.71 (0.45 to 1.1) and cumulative birth: OR=0.95 (0.61 to 1.5)]. Miscarriage was non-significantly higher (11 vs 5).  Interpretation of this study is complicated however by the very large proportion of protocol deviations (see details under ERA below).

Wong 2021 considered women with any indication, regardless of available numbers of follicles or embryos, undergoing their first treatment cycle.  They randomised before the start of down-regulation and compared a policy of cryopreservation of all embryos on day 6 with a strategy of fresh single blastocyst transfer on day 5 followed by cryopreservation of all surplus embryos on day 6. Live birth rate following the first transfer was significantly lower in the freeze-all group - OR (95% CI) = 0.27 (0.11 to 0.66) – with correspondingly lower rates of clinical and ongoing pregnancy. Cumulative rates to 12 months were also significantly lower for their primary outcome of ongoing pregnancy and lower also for cumulative live birth: OR (95% CI) = 0.54 (0.28 to 1.1).  Like Santos-Ribeiro 2020, there were no cases of OHSS in the freeze-all group: 0 vs 3 (3%) requiring hospitalisation.

Current rating amber.
**Recommendation: amber** (conflicting evidence from Wei 2019 and Wong 2021 in women undergoing a first cycle with single blastocyst transfer.  Clear suggestion of safety benefit, in terms of OHSS risk reduction, for selected groups at high risk when the decision is taken early).

## 2. Embryo Glue

The previous review in 2019 covered ten studies, including eight fully reported RCT with a total of over 2600 participants. The overall quality of studies was low with most at high risk of bias.  The largest and methodologically strongest study, Urman 2008, included over 1200 participants and found significantly increased live birth rate with use of embryo glue.

This review considers the additional evidence from Yung 2021. This is a well-conducted and clearly reported trial randomising 550 couples in Hong Kong planning frozen embryo transfer following an unsuccessful or cancelled fresh transfer cycle.  Reported live birth events were almost identical in the two groups: OR=0.98 (0.67 to 1.4) with very similar pregnancy losses, twin rates and obstetric outcomes. Mean birthweight was approximately 200g more in the group allocated to embryo glue (3058g vs 2842g).

Current rating amber.
**Recommendation: amber** (new study not positive but different population (frozen rather than fresh transfers) and wide confidence interval doesn't fully contradict promise of Urman 2008).

## 3. Endometrial Scratching

The previous review included 21 studies reporting on more than 4000 participants as well as two further studies randomising a further 2000 participants from the Netherlands (van Hoogenhuijze) and UK (Metwally) that were pre-publication.

Studies of women undergoing IUI or natural cycles were of generally poor quality but surprisingly consistent in estimating clinical benefit of scratching.

Studies of women undergoing IVF or ICSI cycles were less optimistic. The more recent, larger and higher quality studies suggested a small but non-statistically significant benefit of up to around 6 percentage points.

This review considers the full published data of van Hoogenhuijze and Metwally and four additional trials.

Peer reviewed results for van Hoogenhuijze 2021 and Metwally 2021 confirmed those included in the previous review.  In brief, both conducted the scratch procedure in the mid-luteal phase of the cycle preceding planned first (Metwally) or second (van Hoogenhuijze) cycle of IVF/ICSI in women of good prognosis.  Both were methodologically strong and reported higher success in the treatment arm that did not reach statistical significance.  Metwally reported that one participant of 449 who underwent the procedure did not find it "tolerable". In van Hoogenhuijze, 54% reported symptoms of blood loss, pain or fever with 12 considered "severe" and no hospitalisations.

Ghuman 2020 and Yavangi 2021 both undertook small trials (n=75 per treatment) in women undergoing IUI.  Endometrial scratch was performed on days 6 to 7 of up to three cycles by Ghuman 2020 and on days 19 to 21 of a single cycle by Yavangi 2021. Neither study reported on live birth.  Ghuman 2020 reported cumulative ongoing pregnancy rate: OR (95% CI) = 0.73 (0.24 to 2.2).  Yavangi 2021 reported clinical pregnancy rate: OR (95% CI) = 1.3 (0.58 to 2.8).  Ghuman reported pain scores with a mean of 7 out of 10 during the first cycle of treatment and correspondingly reduced adherence in subsequent cycles.

Berntsen 2020 evaluated endometrial scratch injury during the follicular phase of the cycle preceding a second or subsequent intended cycle of IVF/ICSI. Unfortunately they describe a catalogue of errors in the design, conduct and analysis of their study.  These include erroneous sample size calculation, failing to recruit and running out of funding after extending the study, loss of all follow-up from a site that closed, and differential post-randomisation exclusions combined with a per-protocol approach to analysis. The live birth OR (95%CI) =1.4 (0.67 to 3.0) adds little to the evidence base.

Rodriguez 2020 evaluated endometrial scratch injury during the luteal phase of the cycle preceding an intended fresh cycle of IVF/ICSI using donor oocytes. They reported slightly increased live birth rates: OR (95% CI) = 1.3 (0.85 to 2.0).  There was no reporting of tolerability.

The addition of two further small studies of endometrial scratch during IUI cycles changes little from the previous review. Although both were less positive than previous results in this population they were relatively small studies given the totality of evidence.

The addition of Rodriguez 2020 to the meta-analysis of live birth rates reported by recent, methodologically sound trials contributes 11% of this restricted evidence base and is sufficient to tighten the confidence interval around a small positive effect. Consistent results across the five studies ($I^2$=0%) gives OR (95% CI) = 1.15 (1.00 to 1.32). This suggests, for example, that in a population of women undergoing IVF/ICSI with 35% chance of live birth, endometrial scratch could increase this to between 35% and 41%.

The only one of these studies not to find a (statistically non-significant) benefit was Lensen 2019. Timing of the procedure in this study was left to clinician preference and not recorded, whereas other studies all performed the procedure during the luteal phase of the preceding cycle.  The Committee should consider whether timing is an important factor and note that Lensen 2019 was also the largest study, contributing 31% of the evidence. Omission of this study would marginally strengthen the case: OR (95% CI) = 1.22 (1.03 to 1.45).

It should also be noted that recent studies have reported pain, blood loss and fever associated with the procedure, although not to an extent resulting in hospitalisation.

The committee should consider whether it is biologically plausible that this add-on may affect implantation differentially between IVF/ICSI, where endometrial scratch is typically performed in the preceding cycle,

and IUI/natural cycles, where it is usually performed in the index cycle.  If so, then consideration could be given to providing separate ratings for the two clinical populations.

Current rating: amber
**Recommendation: amber/green** (consistent evidence from multiple, well-designed trials that attains borderline statistical significance but with clear, associated adverse events.

*4. Time lapse incubation systems*

Time lapse incubation involves two distinct processes both hypothesised to deliver clinical benefits.  First, the ability to leave the embryo undisturbed during repeated assessment may be beneficial to the development process.  Independently, the additional information available through time-lapse imaging may bring benefits for embryo selection. Clinical trials reviewed previously fell into three broad categories evaluating effects of:

i) the environment for embryo development (1 safety study without clinical implications);

ii) the embryo selection process (2 studies at high risk of bias reported statistically non-significant benefits); and

iii) the combined effect of the two (4 studies at high risk of bias with contrasting results).

This update identified a protocol published by Chen 2020 addressing effect (i) above.  This study is still in recruitment but plans to randomise 730 women with diminished ovarian reserve who are undergoing their first or second cycle of treatment. The protocol appears of high quality.  Correspondence with authors confirms that recruitment has been delayed but is currently ongoing with 201 participants randomised to date.

Current rating amber.
**Recommendation: amber** (no additional information).

**New Reviews**

*1. Endometrial Receptivity Array*

Just one study was identified for this assessment. Simón 2021 studied women under 37 years old with BMI 18.5 to 30 kg/m$^2$ who were scheduled for blastocyst transfer and had not suffered previous recurrent implantation failure or miscarriages.  They conducted a comparison of 'personalised embryo transfer' based on ERA with two different control groups – elective frozen ET and fresh ET.

Although this was a moderately sized (n=458), multi-centre study its interpretation is compromised by early randomisation.  More than 10% of randomised participants did not proceed to embryo transfer, and over 40% did not receive the allocated intervention.

For live birth after the first transfer, OR=1.3 (0.79 to 2.0) versus frozen and OR=0.90 (0.57 to 1.4) versus fresh transfer.  For cumulative live birth to 12 months these became OR=1.3 (0.82 to 2.0) and OR=1.2 (0.78 to 1.9) respectively.

The paper reported 'per protocol' analyses that were slightly more favourable to the ERA group in each comparison.  It is perhaps also worth noting that miscarriage of clinical pregnancy was most common in the ERA group: 17 (ERA) versus 11 (frozen) versus 5 (fresh).

**Recommendation: amber** (single study suggestive of potential promise but far from conclusive).

DISCUSSION

Caution is required as the assessments above are made from a methodological perspective without expertise in the clinical or scientific context.  Many post-hoc but biologically plausible rationales could be put forward to 'lump' or 'split' categories presented above.

# Annex C: References of reviewed studies

Bold formatting indicates full references added for 2021 update

| Adjunct | Study | DOI/reference |
|---|---|---|
| **Freeze All** | Aflatoonian 2010 | 10.1007/s10815-010-9412-9 |
| | Shapiro 2011a | 10.1016/j.fertnstert.2011.05.050 |
| | Shapiro 2011b | 10.1016/j.fertnstert.2011.02.059 |
| | Magdi 2017 | 10.1016/j.fertnstert.2017.04.020 |
| | Shi 2018 | 10.1056/NEJMoa1705334 |
| | Vuong 2018 | 10.1056/NEJMoa1703768 |
| | Wei 2019 | 10.1016/S0140-6736(18)32843-5 |
| | Stormlund 2020 | 10.1136/bmj.m2519 |
| | **Santos-Ribeiro 2020** | **10.1093/humrep/deaa226** |
| | **Wong 2021** | **10.1093/humrep/deaa305** |
| **Embryo Glue** | Morbeck 2007 | NCT005882250 |
| | Mahani 2007 | EMHJ 2007;13(4):876-80. |
| | Friedler 2007 | 10.1093/humrep/dem220 |
| | Korosec 2007 | RBM0 2007;15(6):701-7. |
| | Hazlett 2008 | 10.1016/j.fertnstert.2007.05.063 |
| | Urman 2008 | 10.1016/j.fertnstert.2007.07.1294 |
| | Dittmann-Muller 2009 | Hum Reprod 2009;24 Suppl 1:167. |
| | Fancsovits 2015 | 10.1007/s00404-014-3541-9 |
| | Singh 2015 | 10.4103/0974-1208.170398 |
| | Zbořilová 2018 | https://europepmc.org/abstract/med/30764616 |
| | **Yung 2021** | **10.1016/j.fertnstert.2021.02.015** |
| **Endometrial Scratching** | Raziel 2007 | 10.1016/j.fertnstert.2006.05.062 |
| | Karimzadeh 2009 | 10.1111/j.1479-828X.2009.01076 |
| | Narvekar 2010 | 10.4103/0974-1208.63116 |
| | Abdelhamid 2012 | 10.1007/s00404-013-2785-0 |
| | Gibreel 2013 | 10.1111/j.1447-0756.2012.02016.x |
| | Parsanezhad 2013 | IRCT:2012082510657NI |
| | Zarei 2014 | IRCT:2012070810210NI |
| | Wadhwa 2015 | J Hum Reprod Sci 2015;8(3):151-8. |

|  | El Khayat 2015 | 10.1016/j.ejogrb.2015.08.025 |
|---|---|---|
|  | Mahey 2015 | 10.1016/j.fertnstert.2015.07.1163 |
|  | Maged 2016 | 10.1177/1933719115602776 |
|  | Goel 2017 | 10.1007/s10815-017-0949-8 |
|  | Mak 2017 | 10.1016/j.rbmo.2017.04.004 |
|  | Aleyamma 2017 | 10.1016/j.ejogrb.2017.05.005 |
|  | Helmy 2017 | 10.1002/ijgo.12178 |
|  | Senocak 2017 | 10.1016/j.jogoh.2017.09.003 |
|  | Ashrafi 2017 | 10.1111/jog.13401 |
|  | Maged 2018 | 10.1002/ijgo.12355 |
|  | Frantz 2019 | 10.1093/humrep/dey334 |
|  | Lensen 2019 | 10.1056/NEJMoa1808737 |
|  | Olesen 2019 | 10.1016/j.fertnstert.2019.08.010 |
|  | **Berntsen 2020** | **10.1016/j.ejogrb.2020.06.034** |
|  | **Ghuman 2020** | **10.1016/j.ejogrb.2020.08.010** |
|  | **Rodriguez 2020** | **10.1007/s43032-020-00204-8** |
|  | **van Hoogenhuijze 2021** | **10.1093/humrep/deaa268** |
|  | **Metwally 2021** | **10.1093/humrep/deab041** |
|  | **Yavangi 2021** | **10.18502/ijrm.v19i5.9255** |
| **Time Lapse** | Kirkegaard 2012 | 10.1007/s10815-012-9750-x |
|  | Kahraman 2013 | 10.1177/205891581200300204 |
|  | Rubio 2014 | 10.1016/j.fertnstert.2014.07.738 |
|  | Goodman 2016 | 10.1016/j.fertnstert.2015.10.013 |
|  | Wang 2016 | J Reprod Med 61(5):254-262 |
|  | Insua 2017 | 10.1016/j.fertnstert.2017.06.031 |
|  | Alhelou 2018 | 10.1016/j.repbio.2017.12.003 |
|  | Yang 2018 | 10.1093/humrep/dey047 |
|  | Kovacs 2019 | 10.1016/j.ejogrb.2018.12.011 |
|  | **Chen 2020** | **10.1093/humrep/deaa268** |
| **Endometrial Receptivity** | **Simón 2010** | **10.1016/j.rbmo.2020.06.002** |

# New technologies in embryo testing

## Details about this paper

| | |
|---|---|
| Area(s) of strategy this paper relates to: | Shaping the future |
| Meeting: | Scientific and Clinical Advances Advisory Committee (SCAAC) |
| Agenda item: | 9 |
| Paper number: | HFEA (11/10/2021) 009 |
| Meeting date: | 11 October 2021 |
| Author: | Victoria Askew, Policy Manager |
| Annexes | NA |

## Output from this paper

| | |
|---|---|
| For information or recommendation? | For recommendation |
| Recommendation: | Members are asked to: <ul><li>Consider the use of new technologies in embryo testing, such as non-invasive testing using artificial intelligence, and the ethical implications of these technologies in fertility treatment.</li><li>Review whether any outputs from the HFEA are required addressing the use of new technologies in embryo testing.</li><li>Advise the Executive if they are aware of any other recent developments.</li></ul> |
| Resource implications: | None |
| Implementation date: | N/A |
| Communication(s): | None |
| Organisational risk: | Low |

# 1.    Introduction

**1.1.**    The two main types of embryo testing are preimplantation genetic testing for monogenetic disease (PGT-M), and preimplantation genetic testing for aneuploidy (PGT-A). In PGT-M, embryos carrying a specific genetic mutation or chromosomal translocation that is prevalent in a patient's family are identified and not transferred. In PGT-A, embryos carrying a common chromosomal abnormality that cause miscarriage or IVF failure are identified and not transferred; this is principally carried out to improve IVF efficiency. Potential safety concerns regarding biopsy and restrictions to only those embryos suitable for biopsy pose limitations. In addition, embryo mosaicism gives rise to false positives and false negatives in PGT-A because the inner cell mass (ICM) cells, which give rise to the foetus, are not tested.

**1.2.**    A third type of embryo testing that has become commercially available over recent years is preimplantation genetic testing for polygenic disorders (PGT-P, also referred to as polygenic risk score (PRS)). 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. PGT-P is not in line with the requirements in the Human Fertilisation and Embryology Act (1990) so is not permitted to take place in the UK. There are many ethical and practical concerns to consider when determining whether this embryo testing is acceptable in the UK.

**1.3.**    At the **February 2020 SCAAC meeting** the Committee discussed new technologies in embryo testing including cells derived from spent culture media, PGT-P and whole genome sequencing. The Committee raised concerns over the accuracy of results derived from non-invasive testing but felt that, if the risks associated with biopsy could be avoided, then non-invasive testing could become more widespread. Further concerns were discussed around testing for polygenic traits not complying with the requirements under the HFE Act (1990) and the need to counselling patients about possible incidental findings. The Executive were able to clarify that the Code of Practice already gives guidance to clinics on considering incidental findings.

**1.4.**    At the last horizon scanning meeting at ESHRE 2021, it was highlighted that the data used for PGT-P is skewed towards those of European descent and there is a potential for both known and unknown pleiotropic effects. There were concerns that the negative effects of limiting the choices of embryos to transfer would outweigh any benefit of scoring embryos for their *potential* risks of certain diseases.

**1.5.**    In December 2020 a **legal case** was brought against an Australian fertility clinic, Monash IVF, by a group of patients who had received a noninvasive technique for pre-implantation genetic testing for aneuploidy. The technique used DNA collected from the spent culture media instead of conducting an embryo biopsy. The patient that originally pursued the lawsuit felt that they had not been informed that PGT-A using noninvasive techniques could return false positive results and this had affected their ability to make an informed choice about the use of their embryos. Monash IVF has since suspended the use of non-invasive PGT-A.

## 2.      Recent studies

### Non-invasive embryo testing

**2.1.**      Chen et al. (2021) preformed whole-genome DNA methylation sequencing to identify the source of embryonic cell free DNA (cfDNA) in spent embryo culture media (SECM). The results demonstrated that SECM cfDNA was derived from blastocysts, cumulus cells, and polar bodies. They identified the cumulus-specific differentially methylated regions (DMRs) and oocyte/polar body-specific DMRs, and established an algorithm for deducing the cumulus, polar body, and net maternal DNA contamination ratios in SECM. The group concluded that DNA methylation sequencing accurately detected chromosome aneuploidy in SECM and distinguished SECM samples with low and high false negative rates and gender discordance rates, after integrating the origin analysis.

**2.2.**      Rubio et al (2020) conducted a study to evaluate the concordance and reproducibility of testing embryonic cfDNA vs trophectoderm (TE) DNA obtained from the same embryo. They also assessed the contribution of the inner cell mass and TE to embryonic cfDNA released to the culture media. 1301 blastocysts underwent PGT-A from 371 patients across 8 different clinics. SECM was collected after at least 40 hours of culture from day 4.  After media collection, conventional PGT-A, comprising TE biopsy and blastocyst vitrification, was performed. Embryonic cfDNA was analyzed blindly after embryo transfer. Embryonic cfDNA analyses were 78.2% (866/1108) concordant with the corresponding TE biopsies. Sensitivity per center ranged from 76.5% to 91.3% and specificity from 64.7% to 93.3%. The false-negative rate was 8.3% (92/1108), and false-positive rate was 12.4% (137/1108). The group concluded that concordances of embryonic cfDNA with TE and inner cell mass (ICM) suggest that the embryonic cfDNA originates from both compartments of the human embryo.

**2.3.**      Yin et al. (2021) evaluated 75 blastocysts donated to research for the full chromosome concordance rates between SECM vs whole blastocysts (WB), and TE biopsy vs WB, as well as sensitivity, specificity and overall diagnostic accuracy. 78.67% (59/75) of the next generation sequencing (NGS) results in the SECM group were interpretable, a significantly lower percentage than their corresponding TE and WB groups (figures?). The group suggested this was due to intrinsically low quantity and poor integrity of DNA from SECM. Differences in concordance rates, including mosaicism and segmental aneuploidies, were 32.2% (SECM-to-WB, 19/59) and 69.33% (TE-to-WB, 52/75), (p < 0.001). Full concordance rates were 27.27% (15/55) in SECM-to-WB, and 76% (57/75) in TE-to-WB (p < 0.001). Collectively, the group found that NGS data from SECM also translated into lower sensitivities, positive predictive value, negative predictive value, overall diagnostic accuracies, and higher negative likelihood ratio.

**2.4.**      Li et al. (2021) analysed 6 years of PGT-A data from a single centre. 3738 blastocysts showed a rate of 14.9% mosaic embryos (544). 60 patients who had no euploid blastocysts opted for a single mosaic embryo transfer, with 50% (30) of these resulting in a clinical pregnancy. The group then conducted a pilot study to re-culture embryos identified as mosaic using TE biopsy. 41 embryos were re-culture for 14-18 hours and the WB, TE re-biopsy and embryonic cfDNA were compared. 35 (85.4%) of the re-cultured mosaic blastocysts showed euploid WB results. All blastocysts previously classified as low degree (20-50%) mosaics were identified as euploid by WB, whereas four of the six putative high degree (50-80%) mosaic blastocysts showed

chromosomal abnormalities. When the group set a mosaicism identification threshold of 50%, the concordance rates of SECM and TE re-biopsies compared with WB were 87.2% and 85% at the overall ploidy level and 98.8% and 98.3% at the chromosomal level, respectively. After adjustment of the threshold for mosaicism, the specificity of cfDNA was 69.7% to 84.8% in terms of overall ploidy and from 96.1% to 98.9% at the chromosomal level.

**2.5.**  The predictive value of the ratio of mitochondrial DNA (mtDNA) to genomic DNA (gDNA) has been considered as a biomarker for embryonic development potential. Zhang et al. (2021) used digital PCR to measure the mtDNA/gDNA ratio in day 3 culture media for 223 embryos. The mtDNA/gDNA ratios were 22.54 (44.66), 31.25 (36.97), and 46.33 (57.11) for Grades A, B, and C, respectively. The ratio increased overall with an increase in embryo fragment content but did not differ significantly between high-, -medium, and poor-quality embryos. mtDNA/gDNA ratio of cleavage stage embryos forming blastocysts was lower (P=0.005). Trends of mtDNA/gDNA ratio differed according to inner cell mass (ICM) and trophectoderm (TE) levels, but not significantly. mtDNA/gDNA ratio in day 3 culture medium was not significantly improved over morphological scores.

**2.6.**  Several MicroRNA (miRNA) biomarkers of successful outcomes such as implantation potential have been identified by different research groups. Acuña-González et al. (2021) investigated MiRNA expression profiles of hsa-miR-21-3p, -24-1-5p, -191-5p, and -372-5p in SECM on day 5 of embryo culture for two groups classified as either successful (n=25) or unsuccessful (n=25) for implantation. There was a 5.2-fold greater expression of hsa-miR-191-5p in the pregnancy-related culture media (p ≤ 0.001) and a 1.6-fold greater level of hsa-miR-24-1-5p (p = 0.043) in the media corresponding to non-pregnant women. No significant difference existed between the two groups hsa-miR-21-3p (p = 0.38) or hsa-miR-372-5p (p = 0.41). The group concluded that hsa-miR-191-5p could be a possible positive biomarker, and hsa-miR-24-1-5p could indicate a poor prognosis.

**2.7.**  Abu-Halima et al. (2020) undertook a study to identify the level of miRNAs in sperm samples and SECM of embryos of different grade to determine their prediction of pregnancy outcomes. 371 miRNAs were screened in 61 patients undergoing ICSI. miR-19b-3p and let-7a-5p were detected consistently in all SECM and sperm samples. The levels of miRNAs were significantly different between SECM of embryos with different quality. The levels of combined SECM and sperm derived miRNAs were also significantly different between different pregnancy outcomes. MiR-19b-3p showed the highest area under the ROC curve values between positive and negative outcomes, with lower levels in both combined SECM and sperm samples associated with a positive pregnancy outcome. The group concluded that miR-19b-3p may serve as a potential biomarker to predict pregnancy outcome.

## Artificial intelligence (AI) in embryo testing

**2.8.**  Lee et al. (2021) conducted a retrospective study to investigate an end-to-end deep learning model in identifying ploidy status through raw time-lapse video. The group used time-lapse videos with a known PGT-A outcome to train a deep learning model, with 80% of the raw videos used for training and testing preformed on the remaining 20%.  With 690 sets of time-lapse video image, combined with PGT-A results, the deep learning model achieved an AUC of 0.74 from the test dataset (138 videos), in discriminating between aneuploid embryos and others (including euploid and mosaic embryos).

**2.9.** Chavez-Badiola et al. (2020) used 1231 static embryo images with known outcomes to train an Embryo Ranking Intelligent Classification Algorithm (ERICA). The group reviewed ERICA's ability to predict euploid embryos in comparison to ploidy prediction against randomly assigned prognosis labels and against senior embryologists, and the algorithms ability to grade euploidy embryos highly. An accuracy of 0.70 was obtained with ERICA, with positive predictive value of 0.79 for predicting euploidy. ERICA had greater normalized discontinued cumulative gain (ranking metric) than random selection (P = 0.0007), and both embryologists (P = 0.0014 and 0.0242, respectively). ERICA ranked a euploid blastocyst first in 78.9% and at least one euploid embryo within the top two blastocysts in 94.7% of cases, better than random classification and the two senior embryologists.

**2.10.** Miyagi et al. (2019) conducted a pilot study to create an AI algorithm that could determine the probability that a blastocyst would lead to a live birth from a still image, using different supervised machine learning approaches. The models were trained using images of 80 blastocysts that led a live birth and 80 blastocysts that led to an aneuploid miscarriage. The most accurate algorithm was logistic regression with L2 regularisation which could predict the probability of becoming live birth with the accuracy of 0.65. The authors summarised that the system showed a possibility that the AI would be feasible for clinical use and may bring benefits to both patients and medical personnel.

**2.11.** Borio et al (2020) developed an AI model based on artificial neural networks (ANNs) to predict the likelihood of achieving a live birth using the proteomic profile of SECM and blastocyst morphology from a static image. The cohort included 213 patients who underwent single blastocyst transfer at IVI Valencia. A single image of each of 186 embryos was studied, and the protein profile was analysed in 81 samples of spent embryo culture medium from patients included in the PGT programme. Three ANN architectures that were developed classified most of the embryos correctly as leading (LB+) or not leading (LB-) to a live birth: 100.0% for ANN1 (morphological variables and two proteins), 85.7% for ANN2 (morphological variables and seven proteins), and 83.3% for ANN3 (morphological variables and 25 proteins). The artificial intelligence model using information extracted from blastocyst image analysis and concentrations of interleukin-6 and matrix metalloproteinase-1 was able to predict live birth with an AUC of 1.0.

## Preimplantation genetic testing for polygenic disorders (PGT-P)

**2.12.** A review by Tellier et al. (2021) summarised the recent developments in PGT-P. Machine learning methods applied to large genomic datasets have led to the creation of polygenic risk scores (PRSs) that can be used to identify individuals who are at highly elevated risk for disease conditions, such as diabetes, high blood pressure and, breast cancer. PRSs can be used to identify which of two individuals is at a lower disease risk, even when these two individuals are siblings from a shared family environment. The relative risk reduction (RRR) from choosing an embryo with a lower PRS can be quantified by using these sibling results. New technology for precise embryo genotyping allows more sophisticated preimplantation ranking with better results than the current method of selection that is based on morphology.

**2.13.** Treff et al. (2020) conducted an analysis of 11,883 sibling pairs to evaluate clinical utility of embryo selection with PGT-P. Results demonstrate simultaneous RRR of all diseases tested in

parallel, which included diabetes, cancer, and heart disease, and indicate applicability beyond patients with a known family history of disease.

**2.14.** A paper by Turley at al. (2021) highlighted factors that lower the predictive power of polygenic scores in the context of embryo selection. The paper goes on to discuss the potential for unintended consequences from PGT-P including selecting for adverse traits, altering population demographics, exacerbating inequalities in society, and devaluing certain traits. The authors conclude there is a need for a society-wide conversation about this technology.

**2.15.** A review by Munday et al. (2021) compared the strength and weaknesses of three models for the regulation of PGT-P in testing for non-disease traits, such as intelligence. The 'disease-based' models, which limit embryo selection to avoiding disease characteristics, 'libertarian' models, where embryo testing and selection remain unregulated, and a novel 'Welfarist Model' which limits embryo selection according to the impact of the predicted trait on well-being. The review highlights that an effective regulatory regime must be in place as soon as the technology is available. If there is no regulation in place, then the market effectively decides ethical issues.

# 3.     Conclusion

**3.1.** There is continued interest for the development of non-invasive methods of embryo testing to determine implantation potential and to maximise the chances of a live birth. cfDNA, mtDNA and miRNA have all been identified as potential indicators of embryo quality that can be obtained from spent culture media. However, studies have come to different conclusions regarding the specificity and efficacy of these methods, showing a need for increased research in this area and larger studies

**3.2.** The use of AI in reproductive medicine is growing, including using both static and time-lapse images to determine the implantation potential and ploidy status of an embryo. However, there is a need for further research around the accuracy of algorithms to make predictions as well as the wider ethical and practical considerations needed for the implementation of AI in the sector.

**3.3.** PGT-P has become commercially available in countries outside of the UK, however it remains controversial with ethical and practical hurdles to its widespread implementation. There is a need for further research and considerations around the impact of its use, especially with non-disease traits such as intelligence.

# 4.     Recommendations

**4.1.** Members are asked to:

- Consider the use of new technologies in embryo testing such as non-invasive testing using artificial intelligence, and the ethical implications of these technologies in fertility treatment.

- Review whether any outputs from the HFEA are required addressing the use of new technologies in embryo testing.

- Advise the Executive if they are aware of any other recent developments.

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