

Prioritisation of issues identified through the horizon scanning process

Strategic delivery: Setting standards Increasing and informing choice Demonstrating efficiency economy and value

Details:

Meeting Scientific and Clinical Advances Advisory Committee (SCAAC)

Agenda item

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Output:

For information or decision? For decision

Recommendation Members are asked to:

- note the issues identified as high priority through the horizon scanning process, including progress of research (since February 2016)
- consider the high priority issues and work recommendations; and
- consider whether advice from additional external advisors would help in achieving the work recommendations.

Resource implications Dependant on the number of issues the Committee agrees to be high priority

Implementation date The Committee work plan for 2017

Communication(s) Work priorities (as defined by the Committee) will be communicated to the Head of Business Planning

Organisational risk Low Medium High

Annexes Annex 1: Briefing on issues that have been identified as high priority through the horizon scanning process
Annex 2: Issues identified through the horizon scanning process (see spreadsheet)

1. Background

- 1.1. The Authority established a horizon scanning function in 2004, the purpose of which is to identify issues that could have an impact on the field of assisted reproduction or embryo research. By identifying these issues, the Authority can be aware of potential licence applications and prepare, if necessary, a policy or position, or relevant patient information.
- 1.2. Issues are identified from journal articles, conferences and contact with experts such as members of the Authority's Horizon Scanning Panel. The Horizon Scanning Panel is an international panel of experts who meet annually and are contacted via email throughout the year.
- 1.3. The horizon scanning process is an annual cycle that feeds into the business planning of the Executive, the Scientific and Clinical Advances Advisory Committee (SCAAC) and the Authority's consideration of ethical issues and standards. The issues identified in this cycle of the horizon scanning process will be incorporated into the 2017/18 business plan and workplan for the Executive, SCAAC and the Authority.

2. Prioritisation process

- 2.1. A full list of all issues identified since February 2016 can be found in Annex B to this paper.
- 2.2. To help with the business planning process, it is important for the Executive to be fully aware of which issues members consider to be of high priority. New techniques which have been identified this year have been categorised as low, medium or high priority using the following criteria:
 - Within the HFEA's remit
 - Timescale for likely introduction (2-3 years)
 - High patient demand/clinical use if it were to be introduced
 - Technically feasible
 - Ethical issues raised or public interest
- 2.3. New techniques are considered to be high priority if they meet at least three of these criteria and medium if they meet at least two. Whilst low priority issues are unlikely to impact on research or treatment in the near future, published studies in these areas will continue to be collected and considered as part of the horizon scanning process.
- 2.4. High priority is also given to established techniques or issues which fall within the HFEA's remit and require ongoing monitoring or provision of patient information.

3. High priority issues

3.1. The Executive considers the following topics to be of high priority for consideration in 2017/18: Briefings about these issues, based on horizon scanning findings, can be found at Annex A.

- a) Use of ICSI
- b) Mitochondrial donation
- c) Genome editing
- d) Fertility preservation (tissue transplantation)
- e) Embryo culture media
- f) Health outcomes of children conceived from ART
- g) Alternative methods to derive embryonic and embryonic-like stem cells
- h) New technologies in embryo testing (including embryo biopsy)
- i) Treatment add ons

3.2. Briefings have been written about issues a) to d), based on horizon scanning findings, these can be found at Annex A. Briefings have not been written for the remaining high priority areas, as these topics are either standing items that are considered by the committee every year, or they have already been considered by the committee recently.

3.3. Following discussions on the briefings, and their priority status, the Executive asks the committee to consider whether any of the priorities should be amended.

Annual review of treatment add ons

3.4. The Executive has, for the first time, produced patient information about treatment add ons in consultation with SCAAC. This includes a visual indicator of the quality of evidence supporting an add on, in the form of a traffic light system. As new research is published it will be necessary to review our assessment of the quality of evidence to ensure that our patient information and traffic light system remain up to date.

3.5. As part of the annual horizon scanning process, the Executive will collate published research relating to treatment add ons and ask the committee to assess whether the current patient information or traffic light rating for any treatment add ons needs to be reviewed. The Executive will then seek an independent assessment of the quality of evidence for the treatment add on and consider whether any amendments are required.

3.6. Based on the research collated through the horizon scanning process, the committee will also be asked if any new treatment add ons need to be added to the HFEA patient information. If a need for new patient information is identified, the Executive will seek an independent assessment of the quality of evidence for the particular add on and assign a traffic light rating to it.

4. Recommendations

4.1. Members are asked to:

- Note the issues identified as high priority through the horizon scanning process, including the progress of research (since February 2016)
- Consider the high priority issues and work recommendations; and
- Consider whether any advice from additional external advisors would help in achieving the work recommendations

5. Next steps

- 5.1.** Following discussions by the committee, the priority issues, in addition to other work areas, will be used to formulate the committee workplan for 2017/18. Any areas of work which are likely to go beyond the committee's scope, and may impact on the work of other Authority committees, will be considered for inclusion in the business plan for 2017/18.

Annex A: Briefings on issues that have been identified as high priority through the horizon scanning process

1. Use of ICSI

Background

- 1.1.** Intracytoplasmic sperm injection (ICSI) is the process of injecting a single sperm into an egg. ICSI techniques currently account for around two thirds of ART treatments in Europe. In recent years, experts have been debating whether ICSI is being used appropriately.
- 1.2.** In 2009 SCAAC considered the use of ICSI and the potential risks. The HFEA issued guidance to licensed fertility clinics regarding information which they should provide to patients about the risks involved with ICSI (e.g. risks of eggs being damaged in the procedure, risk of miscarriage, risk of embryos/children having genetic abnormalities, imprinting disorders and male infertility being passed onto the next generation). Research exploring the impacts of ICSI has continued to grow and SCAAC have monitored developments through their horizon scanning functions looking at health outcomes in ART children. A summary of recent discussion in this area is provided below.
- 1.3.** In 2012, Prof Michael Davies presented his work to SCAAC, exploring the extent to which birth defects in children born from fertility treatment may be explained by underlying parental factors. The risk of birth defects associated with ICSI remained increased after multivariate adjustment, although the possibility of confounding factors could not be excluded. The committee highlighted the need to consider the risks of birth defects in IVF, and particularly ICSI, as an important area of research. The committee raised concerns about the extrapolation of the study's findings, suggesting that the study was confined to two regionally specific sites and a small sample size. The committee agreed that this was an important area of research and suggested that larger long term follow-up and observational studies were required to more comprehensively explore any possible links between birth defects and IVF/ICSI.
- 1.4.** In the same year, a study by Hodez-wertz et al. (2012) determined whether the use of ICSI in couples who previously underwent ICSI cycles elsewhere could be decreased without compromising the pregnancy rate. The group retrospectively analysed the records of 149 fresh, in vitro fertilisation-embryo transfer cycles in patients who underwent ICSI elsewhere and subsequent fertilisation by insemination only (all insemination group) or half insemination and half ICSI. They compared fertilisation, implantation, and clinical pregnancy and live birth rates. The group found no statistically significant difference in the live birth rate between the two groups. This study therefore suggests that stringent criteria for ICSI may not compromise the clinical outcome and fertilisation can be achieved whether or not ICSI is used.

- 1.5.** In 2014 SCAAC raised the use of ICSI as a high priority issue and it was agreed that the committee would reconsider this topic on publication of the most recent and relevant professional body guidance. The most recent update on this guidance is that it is due for publication in 2017.

Summary of developments

- 1.6.** In 2015, Boulet et al. analysed data from the US National Assisted Reproductive Technology Surveillance System to explore trends in the use of ICSI between 1996 and 2012. They identified 1,395,634 fresh IVF cycles, of which 908,767 (65.1%) used ICSI and 486,867 (34.9%) used conventional IVF. Male factor infertility was identified in 35.8% of fresh IVF cycles. The team found that in the presence of male factor infertility, reproductive outcomes of fresh IVF cycles using ICSI were similar to outcomes using conventional IVF. In cycles using ICSI without male factor infertility, the team identified “*small but significant*” reductions in implantation, pregnancy, live birth and multiple live birth, compared with cycles using conventional IVF without male factor infertility.
- 1.7.** In 2016, Belva et al. published the first assessment of fertility in men aged between 18 and 22 years, who were conceived using ICSI for severe male factor infertility. The study reports the results of a single semen sample analysis in 54 adult men who were conceived by ICSI and 57 spontaneously conceived men. The men conceived by ICSI were found to have significantly lower median sperm concentration, total sperm count and total motile sperm count compared to their spontaneously conceived peers. Although the sample size for this study was small, it provides the first indication that male infertility may be passed on to the next generation when boys are conceived by ICSI.
- 1.8.** The International Committee for Monitoring Assisted Reproductive Technologies world report: Assisted Reproductive technology 2008, 2009 and 2010 was published by Dyer et al. in 2016. The report showed that ICSI was used in around 66% of aspiration (egg collection) cycles, however, ICSI was used in 100% of cycles in the Middle East, compared with 55% in Asia and 65% in Europe. The authors noted that investigation into who ICSI is a preferred fertilisation technique in a number of countries, particularly in Latin America and the Middle East, is warranted.
- 1.9.** Tannus et al. (2017) investigated whether ICSI improves reproductive outcomes compared with conventional IVF when used for male factor infertility in women aged 40 years and older. This retrospective, single centre study included a total of 745 women: 490 women underwent ICSI and 255 had conventional IVF. All women were at least 40 years old at the beginning of ovarian stimulation and their male partner had normal sperm parameters according to the World Health Organisation criteria. The results showed that, after controlling for confounders, the live birth rates between the ICSI and conventional IVF groups were similar. The authors suggest that there is no advantage of ICSI over conventional IVF in women aged 40 years and over when used for non-male factor infertility. This study, whilst retrospective in

nature, and with a small sample size, prompts the question: why ICSI is being used for couples without male factor infertility?

Impact

- 1.10.** Despite ICSI being used in around 66% of IVF cycles, it remains unclear what the long term effects may be on those born as a result of this technique. It is unclear what the clinical indication for ICSI may be in cases where there is no male factor infertility, particularly when donor sperm is used. There is some indication that the use of ICSI may increase the risk of birth defects and that male infertility may be passed on to the next generation. It is important to understand what the full implications are of using ICSI as an alternative to conventional IVF and why, in some areas, this technique has become the 'go-to' treatment option for couples without any male factor infertility.

Level of work recommendation

- 1.11.** The committee is asked if they would like to see a wider literature review exploring the risks of ICSI and whether this technique is being used appropriately. The committee is also asked if they want to continue to delay consideration of this topic until new professional body guidance is published. If this topic is considered further, the Executive will draft information for patients with input from the committee and professional bodies.

References

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2. Mitochondrial donation

Background

- 2.1.** Mitochondrial malfunction caused by mutations in mitochondrial DNA (mtDNA) is a significant cause of several serious multi-organ diseases. Until recently, many families with such inherited diseases had no effective treatment options for avoiding transmission of these disease to their offspring. However, two new techniques, maternal spindle transfer (MST) and pronuclear transfer (PNT) now offer the prospect of preventing such serious disease through the use of assisted conception.
- 2.2.** In February 2015 the UK Parliament approved the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015, making MST and PNT to avoid serious mitochondrial disease lawful treatments. The Regulations came into force in October 2015, along with the HFEA's system for licensing clinics to use mitochondrial donation and for approving individual applications. However, the Authority agreed it would only accept applications once an independent panel of experts were satisfied that MST and PNT were sufficiently safe and efficacious to move from research to clinical treatment.
- 2.3.** In 2016, two research groups published studies (Hyslop et al.; Yamada et al.) which showed that significant progress had been made in addressing recommendations that had previously been set out by the expert panel in their 2014 report. The expert panel was therefore reconvened in July 2016 to assess the current state of the research, with particular reference to whether the 2014 experimental recommendations had been met. A third directly relevant paper was also considered by the panel prior to publication of their report in November 2016. Based on the research they reviewed, the panel recommended that it is now appropriate to offer mitochondrial donation techniques as clinical risk reduction treatment in carefully selected patients.
- 2.4.** In December 2016 the Authority met to consider the findings of the expert panel. The Authority made the decision to approve the use of mitochondrial donation in certain, specific cases where PGD is inappropriate or likely to be unsuccessful. This decision means that, for the first time, clinics are able to apply to vary their licence to permit the use of MST or PNT in clinical treatment, once a clinic has varied their licence they can then apply on a patient by patient basis for permission to treat individual patients.

Summary of developments

- 2.5.** Yamada et al. (2016) carried out MST using human eggs that were then artificially activated. They reported that the process of oxidative phosphorylation was normal in differentiated cell types from embryonic stem (ES) cell lines derived from MST embryos, despite using mtDNA combinations from distinct haplogroups. Yamada et al found that in the majority of ES cell lines, the levels of mtDNA that was carried over along with the maternal spindle remained low. However, they observed in one of the eight cell lines produced that the carried

over mtDNA levels increased over time, a phenomenon that has been referred to as 'reversion'.

- 2.6.** Kang et al. (2016) carried out MST using eggs carrying mutated mtDNA, they used two sets of controls: embryos created using MST between donated eggs without mutated mtDNA and unmanipulated eggs fertilised by ICSI. The team worked on improving the efficiency of MST, with factors including embryo survival, blastocyst development and quality being similar between MST eggs and controls. Whilst the average level of carryover was low at less than 1%, Kang et al. also observed that in a minority of cases, the level of carried over mtDNA increased over time in stem cells derived from MST embryos.
- 2.7.** Also in 2016, Hyslop et al. published their work refining their PNT procedure, showing that better outcomes were possible when PNT was undertaken shortly after in vitro fertilisation (so called, 'early PNT'). The team also showed that vitrification of patient eggs is likely to increase efficacy of PNT. Similar to the results of Kang et al. and Yamada et al., Hyslop et al. observed an increase in levels of carried over mtDNA in a minority of ES cell lines derived from PNT embryos.
- 2.8.** The first live birth following MST in human eggs was reported in 2016 by Zhang et al. who carried out the treatment to prevent the mother from passing on a serious mitochondrial disease to her child. The team from New York travelled to Mexico to carry out the treatment and the baby is reported to be doing well with low levels of mutated mtDNA in several tissues at five months of age. The full details of the treatment cycle have not yet been published.
- 2.9.** In October 2016 it was reported that PNT had been used as a treatment for infertility at a clinic in Ukraine (Coghlan, 2016). The Ukrainian team reported carrying out PNT in two women, both of whom were pregnant. In early 2017 it was reported that the first of the two women had given birth to a healthy baby.

Impact

- 2.10.** The process of making MST and PNT lawful treatments in the UK for the avoidance of serious mitochondrial disease has been closely followed by scientists, clinicians and patients across the world. Research published in 2016 shows that in a minority of ES cell lines derived from mitochondrial donation embryos, the level of carried over mtDNA increases over time. It remains unclear whether this phenomenon occurs as a result of MST and PNT, or if it is an artefact of ES cell biology. If this reversion is observed in embryos, it could mean that children born following MST or PNT may still be affected by mitochondrial disease. As this treatment is brought into clinical practice, it will be important to continue to monitor scientific and clinical research in this area, and to closely monitor the progress of any children born.

Level of work recommendation

- 2.11.** The committee will be asked to monitor any further developments in the scientific and clinical literature relating to mitochondrial donation techniques. In order to aid discussions on this topic, the committee is asked if they would like

to invite any specialist speakers to present at the relevant meeting and take part in a discussion with the committee. The Executive will update the committee on the analysis of any follow up data they receive on children born using MST or PNT. These discussions will help the Executive in their monitoring of mitochondrial donation and highlight any possible issues with the techniques which may impact on their clinical use.

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3. Genome editing

Background

- 3.1. Recent developments in genome editing technologies provide the potential to insert, delete or modify DNA with increased specificity and efficiency. This process was developed in human somatic gene transfer. It has been discussed by the committee who considered the potential for pluripotent stem cells that may be used to prevent disease and also provide potential therapeutic applications. More recent research has explored techniques that may be used for human germ line modification.
- 3.2. At the forefront of genome editing technologies are techniques such as CRISPR-Cas9, which hold such promise due to their targeted approach, simplicity, efficiency, affordability and speed.
- 3.3. Genome editing of embryos for use in treatment is illegal in the UK. It has been permissible in research since 2009, provided that the research project meets the criteria set out in the Human Fertilisation and Embryology Act 1990 (as amended) and is carried out under an HFEA licence. In 2016 the Authority approved the research licence application to use CRISPR-Cas9 in human embryos. Despite this technology not being legal in clinical practice, it is important to monitor the progress of research in this area.

Summary of developments

- 3.4. At SCAAC's June 2015 meeting the Committee discussed the recent research conducted by a Chinese group using CRISPR-Cas9 (Liang et al.). The group demonstrated that CRISPR-Cas9 could effectively cleave the endogenous β -globin gene (HBB). However, the efficiency of homologous recombination directed repair (HDR) of HBB was low and the resulting edited embryos were mosaic. The research group highlighted that their work demonstrated a need to further improve the fidelity and specificity of this technique. The Committee agreed that this topic should be noted as high priority and developments in this area monitored.
- 3.5. Basic research into CRISPR-Cas9 efficacy is moving quickly. In 2015, Slaymaker et al. conducted research seeking to improve the specificity of Cas (the RNA-guided endonuclease) which is used as a genome editing tool. Cas9 creates double-strand breaks at targeted genomic loci complementary to a short RNA guide. However, Cas9 can cleave off target sites. The group used structure-guided protein engineering to improve the specificity of *Streptococcus pyogenes* Cas9 (SpCas9). They demonstrated that "enhanced specificity" SpCas9 (eSpCas9) variants reduce off-target effects and maintained robust on-target cleavage by utilising targeted deep sequencing and unbiased whole-genome off target analysis, to analyse Cas9-mediated DNA cleavage in human cells. Therefore, this study highlights that eSpCas9 could be useful for genome editing applications requiring a high level of specificity.

- 3.6.** A further study (Yu et al. 2015) looked at the bacterial CRISPR-Cas9 system as a potential tool for sequence-specific gene knockout through non-homologous end joining (NHEJ). They developed a reporter-based screening approach for high-throughput identification of chemical compounds that can modulate precise genome editing through homology-directed repair (HDR). The group use small molecules that have been identified to enhance CRISPR-mediated HDR efficiency, 3- fold for large fragment insertions and 9-fold for point mutations. The group also found that a small molecule that inhibits HDR can enhance frame shift insertion and deletion (indel) mutations mediated by NHEJ. The identified small molecules were shown to function well in diverse cell types with minimal toxicity and may therefore provide a straightforward and effective strategy to improve genome engineering applications.
- 3.7.** In 2016 the Nuffield Council on Bioethics issued an ethical review on genome editing, which considers the impact of recent advances in this area. Two priority areas were identified by Nuffield: human reproduction and livestock. Working groups have been formed to consider these areas further and to develop policy recommendations.

Impact

- 3.8.** Currently there is only one research project taking place in the UK using genome editing techniques on human embryos. The benefits of new technologies such as CRISPR-Cas9 in gene editing mean that the potential to modify human germ cells to be disease free could exist. For the present, research focusses on improving the specificity of the gene editing tool and improving its efficiency.

Level of work recommendation

- 3.9.** The Executive will keep abreast of the progress of research in this area to ensure that developments are monitored. The Committee is, therefore, asked to consider whether there are any further studies or developments in the area and identify particular concerns or issues that should be highlighted.

References

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4. Fertility preservation (tissue transplantation)

Background

- 4.1. Fertility preservation may be carried out for a number of reasons: to delay parenthood until a person is ready to start a family, to allow treatment of a medical condition which may affect future fertility (such as cancer treatment), and in cases where a person is at risk of injury or death. The two main methods of fertility preservation are freezing of eggs, sperm or embryos and freezing of ovarian or testicular tissue.
- 4.2. The committee last discussed fertility preservation in February 2015, when Professor Helen Picton was invited to discuss developments in egg and sperm freezing, tissue transplantation and upcoming research. The committee discussed egg freezing in detail, with Prof Picton explaining that clinical research indicates that vitrification is the optimum method for freezing mature eggs. The committee also discussed ovarian tissue banking; Prof Picton explained that there is an increased understanding of the mechanisms involved in ovarian tissue damage and follicular loss in the human ovary. At this time, slow freezing was the optimum method for ovarian tissue freezing, however, research was moving towards the use of vitrification.
- 4.3. In recent years, research into fertility preservation has continued to progress, particularly in relation to tissue transplantation. There has also been increased media attention around egg freezing for social reasons.
- 4.4. In 2015 a multidisciplinary group formed the 'Fertility Preservation UK' network, which became a British Fertility Society Special Interest Group in 2016. The aim of the group is to develop and promote best practice in the reproductive care of people with cancer and chronic disease. The Royal College of Nursing (RCN) have also convened a working group (which includes the HFEA) to develop a leaflet for healthcare professionals caring for patients who will be receiving treatment that could adversely affect their fertility. This is under development and the aim of the document will be to provide information and direction for this group of professionals.

Summary of developments

- 4.5. Demeestere et al. (2015) reported the first live birth after autograft of ovarian tissue that was cryopreserved during childhood. Ovarian tissue was removed and frozen at age 14 (prior to menarche but after the onset of puberty) due to treatment for homozygous sickle cell anaemia. Ovarian tissue transplantation was carried out when the woman was 24 years old. Regular menstruation was reported during the first two years after transplantation and the woman had a spontaneous pregnancy in 2014 and delivered a healthy baby boy.
- 4.6. In 2016 the first baby was born following transplantation of ovarian tissue that was removed and frozen before puberty (BioNews 2016). The ovarian tissue was frozen at the University of Leeds when the patient was aged nine, prior to treatment for beta thalassaemia. The tissue was then transplanted back to the

woman by a Danish team, and the woman gave birth to a healthy baby at age 24 years.

- 4.7.** Further evidence supporting the efficacy of ovarian tissue freezing in pre-pubertal girls was published by Abir et al. (2016). The team carried out a prospective study on 42 paediatric females with cancer, 22 patients had not yet undergone chemotherapy and 20 patients had already had chemotherapy. Follicle containing ovarian tissue, as well as eggs which were matured in vitro, were obtained from patients as young as two or three years old. The authors conclude that vitrified in vitro matured eggs may serve as an important gamete source in paediatric female cancer patients.
- 4.8.** Wallace et al. published a review article in 2016 on fertility preservation in pre-pubertal girls with cancer, with particular discussion on the role of ovarian tissue freezing. The authors highlighted that ovarian tissue freezing for children with cancer remains experimental, with consent and ethical issues needing to be explored before this treatment can be offered more frequently. The authors present a framework for patient selection which has been shown to be effective in identifying patients at high risk of ovarian insufficiency and who can be safely offered ovarian tissue freezing.
- 4.9.** Meirow et al. (2016) published a prospective cohort study evaluating transplantations of frozen ovarian tissue in cancer survivors. The team treated 20 patients who had ovarian tissue frozen between 14 and 39 years old. 16 pregnancies were reported within the group after ovarian tissue transplantation, resulting in 10 live births with two pregnancies ongoing at the time of publication. The authors reported that all the patients who underwent ovarian tissue freezing and transplantation, remained cancer free. The authors also report that the results from this study led Israel's national ethics and professional authorities to decide not to consider ovarian tissue freezing an experimental method of fertility preservation.
- 4.10.** In 2016 the HFEA published egg freezing statistics as part of its 2014 Fertility Trends and Figures report. The report showed that the number of women storing their eggs has increased substantially since 2005, with the most rapid growth occurring once vitrification became more widely available around 2010. The most common single reason given for egg freezing was due to having no male partner. The overall live birth rate per thawed cycle was 14%, the birth rate per cycle was lower than that for treatment using fresh eggs or thawed frozen embryos. Since 2001, fewer than 60 babies have been born to patients storing and thawing their own eggs. This is a low number considering the attention egg freezing receives, but this is a new, emerging treatment area which the HFEA will continue to monitor.

Impact

- 4.11.** Fertility preservation and the reasons why people choose to preserve their fertility remains a much discussed topic in the field of assisted reproduction. As patients increasingly consider egg, sperm and embryo freezing a feasible method for fertility preservation, the Executive needs to continue to monitor

developments in this field in order to provide up to date information. It is also important to monitor developments in ovarian and testicular tissue freezing as a method for fertility preservation for cancer patients (including pre-pubertal children) and to consider any regulatory issues which may arise if tissue transplantation becomes more common.

Level of work recommendation

- 4.12.** The committee is asked whether they think the time is right for a more detailed literature review on fertility preservation, and which topics should be the focus of any such review. If this topic is considered in more detail, the Executive will evaluate whether any update patient information is required.

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