Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1435.1 - Processing and cryopreservation (freezing) of ovarian tissue and thawing and preparation of ovarian tissue for ovarian tissue transplantation following gonadotoxic treatment

Applicant: **Kids Cancer Centre**

Date of MSAC consideration: **MSAC 76th Meeting, 1-2 August 2019**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

A resubmission requesting Medicare Benefit Schedule (MBS) listing of processing and cryopreservation of ovarian tissue was received from the Kids Cancer Centre by the Department of Health.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC did not support public funding for processing and cryopreservation (freezing) of ovarian tissue (complete or partial ovary removal) for fertility preservation either prior to, or after, gonadotoxic treatment for malignant or non-malignant conditions, and the thawing and preparation of ovarian tissue transplantation following gonadotoxic treatment. MSAC remained concerned about the weak evidentiary base, the ongoing storage costs and the long-term safety for mothers and babies. In particular, concerns remained about the risk of stored ovarian tissue containing malignant cells.

Consumer summary
The Kids Cancer Centre applied for public funding for ovarian tissue cryopreservation (OTC) and ovarian tissue transplantation (OTT) for female children, adolescents and adults under 40 years of age who are having treatment that can damage ovarian tissue (for example, cancer treatment), and who may want to become pregnant later. OTC and OTT are processes that allow ovarian tissue to be frozen, thawed and then placed back into the woman at a later stage. Funding for this application was previously requested in 2018. At that time, MSAC did not support funding because there was not enough evidence to show that the treatment was safe and effective. MSAC asked the applicant to provide more evidence. This resubmission did

Consumer summary
not provide the extra evidence that MSAC requested, also no economic analysis was provided. **MSAC's recommendation to the Commonwealth Health Minister** MSAC accepted that there is a clinical need for these procedures. MSAC did not support MBS funding of OTC and preparation for OTT because it is not clear how effective these processes are and there are still some safety concerns with risk of stored ovarian tissue containing malignant cells. MSAC noted that no economic analysis was provided and it is also uncertain how many people might use these procedures, and therefore how much this would cost the healthcare system.

3. Summary of consideration and rationale for MSAC's advice

Application 1435.1 is a resubmission requesting the creation of multiple MBS items relating to the processing and cryopreservation of ovarian tissue (OTC) as well as thawing and preparation of ovarian tissue for ovarian tissue transplantation (OTT) following gonadotoxic treatment. MSAC noted that there is a clear clinical need for OTC and OTT. It is the only option for:

- females immediately before they have gonadotoxic treatment;
- pre-pubertal girls (with no mature oocytes); and
- women when their risk of infertility is high (in association with mature oocyte preservation).

Overall, MSAC noted the resubmission did not contain the additional information that MSAC requested after its initial consideration in March 2018.

MSAC noted that the clinical effectiveness remains uncertain for OTC and OTT. Although five studies have been published since the original application in 2018, four of these were case series or case reports (that is, low quality evidence).

MSAC noted that the chance of successful pregnancy after OTT is currently about 30%, and the chance of a live birth is about 22% (Anderson et al. 2017).

MSAC noted the agreed clinical management algorithms for both pre and post gonadotoxic treatment were not amended in the resubmission to demonstrate where OTT would be placed in the pathway.

MSAC noted that OTC procedure has acceptable safety in post-pubertal females. However, MSAC is concerned about the risk of stored ovarian tissue containing malignant cells that survive cryopreservation and are then re-transplanted (especially haematological or ovarian cancers). MSAC requested a protocol demonstrating how malignancy in cryopreserved tissue is ruled out. The applicant described procedures, but without any references or any statement that the procedures are a consensus and considered to be best practice. The applicant's pre-MSAC response stated that the malignancy protocols are standard international practice based on expert international consensus. However, MSAC noted the literature indicated that OTC cannot be guaranteed that it is completely safe in terms of re-transplanting malignant cells (Andersen et al 2018).

MSAC noted that the applicant's pre-ESC response stated that it will take 20 years to attain long-term safety data for pre-pubertal OTC patients. MSAC noted that even with new evidence, data on the number of live births after OTC in post-pubertal females remain limited, and the uptake of OTT is estimated at around 4%.

MSAC noted that the current Australian and US guidelines state that OTC and OTT are experimental techniques. MSAC acknowledged that more data are being collected. Nevertheless, MSAC noted that any patients using these techniques must understand the risks associated with it.

MSAC noted that there are high out-of-pocket costs for storage, because the period of storage can be many years if the patient undergoes OTC when they are young.

MSAC noted that no economic analysis was done, despite MSAC requesting (in 2018) that the applicant provide incremental cost per extra live birth. MSAC noted that a comparative study in post-pubertal patients is now available, which could provide some data (although the evidence is of low quality). MSAC also noted that the costs to the MBS are sensitive to estimated use of OTC, which is uncertain.

MSAC noted that the pre-MSAC response was only received on the day of the MSAC meeting.

MSAC suggested that, if this application is resubmitted, it go through PASC and focus on post-pubertal females, where more evidence is available and consider only looking at OTC rather than OTC and OTT together. In addition, it may help to wait for data to become available through the Australasian Oncofertility Registry. MSAC also recommended it be done through a department-contracted assessment rather than an applicant-developed assessment.

MSAC noted the NSW Government announced a $42 million package to fund *in vitro* fertilisation (IVF) including fertility preservation for young patients with cancer. MSAC considered that the States and Territories should be made aware that OTC/OTT is still considered experimental with uncertain clinical effectiveness and of the safety concern with the risk of re-transplanting malignant cells.

4. Background

Application 1435 was considered by MSAC at its March 2018 Meeting. MSAC did not support MBS funding for the processing, analysis and cryopreservation of ovarian tissue (OTC) to preserve fertility in females undergoing potentially gonadotoxic treatment. While MSAC acknowledged the merit of such a service, as it is the only option for fertility preservation in pre-pubertal women, it did not support MBS funding due to uncertain clinical effectiveness and unresolved safety concerns, particularly risk of malignancy.

MSAC advised that any resubmission should include:

- a protocol showing how malignancy in the cryopreserved tissue is ruled out;
- evidence of clinical benefits and quality of life information;
- further data on utilisation including proportion of females who subsequently use the preserved tissue; and
- the incremental cost per extra live birth (inclusive of all associated costs).

5. Prerequisites to implementation of any funding advice

As at July 2017, there were 34 different assisted reproductive technology (ART) components listed on the ARTG, primarily equipment items, and over 100 culture mediums listed relevant to IVF, which have relevance to this application.

Accreditation for OTC/OTT
All fertility and andrology centres in Australia are licensed by the Reproductive Technology Accreditation Committee (RTAC) Certification Scheme, developed by the Fertility Society of Australia and independently audited by Joint Accreditation System of Australia and New Zealand (JAS-ANZ). RTAC is an independent body responsible for ensuring standards are met by all fertility and andrology clinics in Australia.

National Association of Testing Authorities (NATA) is a technical accreditation provider to laboratories and is formally recognised by the Federal Government as the national authority for accreditation of laboratories conducting tests and measurements in all technical fields. The application stated if and when oncofertility items are covered by Medicare, NATA will extend its accreditation to the relevant cryopreservation procedures.

6. Proposal for public funding

The application requested three new MBS item numbers which include: (i) two MBS item numbers to cover the processing and freezing components of cryopreservation of ovarian tissue, (partial or whole ovary removal) in females aged between 0 and 40 years who are scheduled to undergo, or have completed gonadotoxic treatment and (ii) one MBS item number for thawing and preparation of ovarian tissue prior to ovarian tissue transplant (OTT) in patients wanting to have a biological pregnancy if they subsequently become infertile (Table 1; descriptor notes below proposed MBS items).

Note, the patient or their family would still be required to pay for storage fees.

Table 1 Proposed MBS item descriptors for processing and cryopreservation of ovarian tissue, prior to, or following completion of gonadotoxic treatment

Category 3 – Therapeutic Procedures
Proposed new MBS item 1 Processing and cryopreservation of a partial ovary for fertility preservation treatment for females ≤40 years old, before or after completion of gonadotoxic treatment, at diagnosis or relapse. Proposed fee: $608.64, Benefit: 75% = $456.48
Proposed new MBS item 2 Processing and cryopreservation of a whole ovary for fertility preservation treatment for females ≤40 years old, before or after completion of gonadotoxic treatment, at diagnosis or relapse. Proposed fee: $944.82, Benefit: 75% = $708.62
Proposed new MBS item 3 Thawing and preparation of ovarian tissue for OTT Proposed fee: $619.75, Benefit: 75% = $464.81

Category 3 – Therapeutic Procedures
Explanatory notes for all proposed item numbers: **Preparation of the cortical ovarian tissue** The ovarian tissue is prepared prior to freezing by dissecting apart the surface (cortical) tissue containing the follicles, and the inner part, mainly circulation and support tissue. The surface tissue is subsequently dissected into 1mm thick slices to facilitate movement of the cryoprotectants (anti-freeze solutions). This is a manual procedure. **Freezing of the cortical ovarian tissue** The slices of ovarian cortical tissue are exposed to cryoprotectants to remove water from the cells and placed in vials in an automated freezing machine, which gradually reduces temperature at a controlled rate over time to -150 °C. The vials are then stored in a large tank containing liquid nitrogen at a temperature below -150 °C. **Thawing and preparation of ovarian tissue for OTT** The tissue is rapidly thawed followed by stepwise dilution of the cryoprotectants to achieved controlled rehydration of the tissue. The small tissue pieces are then sutured together for transplantation. **Tissue Histology** Protocols are already available for the handling and management of ovarian tissue on collection to ensure that they have normal pathology and are not contaminated by malignant cells, the technique varies by cancer type and this includes histology, immunohistochemistry, immunophenotyping, PCR for molecular markers Medicare item numbers provided. Where necessary low level of contaminating malignant cells can be evaluated using a xenografting system. Ovarian tissue is not transplanted (OTT) without a re-assessment of ovarian contamination being undertaken. This allows for improvements in minimal disease testing over time and review of the initial testing especially if this was done a long time before transplantation (OTT) of tissue occurs. Tissue will still be able to be collected from patients who have malignant deposits in the abdomen/pelvis, if they are well enough to undergo an anaesthetic and surgical procedure, and achieve fertility preservation through new techniques for in vitro-maturation of oocytes and follicles isolated from the ovarian tissue. Currently around half of immature oocytes collected from ovarian tissue will following IVM mature in the laboratory and with recent advances in IVM this is expected to improve. This approach has resulted in live births in two cases of ovarian cancer[166, 167] where no other options were possible. Recently immature follicles have been isolated from pre-pubertal tissue and successfully matured in the laboratory in order to be used for IVF[168]. These options allow for patients with malignant contamination to be able to use this technique. Of the 131 published births worldwide, there has not been a higher relapse rate in patients who have had ovarian tissue re-implanted and there has not been a single reported case of recurrence associated with OTT. OTT is currently not MBS listed and may incur cost similar to embryo/oocyte thawing; (MBS item 13218 – $793.55), laparoscopy (MBS item 35638), anaesthesia (MBS item 20706) and surgical assistance (MBS item 51303).

The Critique stated that the two items for cryopreservation differ from the previous Contracted Assessment in the age restriction (previously broader at 0-45 years) and fees proposed. No justification has been given for either change. In the pre-MSAC response, the Applicant explained the age was reduced to 0-40 years based on research evidence showing that with an increased age there is a reduction in egg quality and the rate of successful conception with grafted tissue taken from older women in significantly lower. Those women who do get pregnant in this age group also have an increase rate of miscarriage and other pregnancy complications.

7. Summary of Public Consultation Feedback/Consumer Issues

No further consultation feedback was received since Application 1435 was considered by ESC in Oct 2017.

Previous feedback received during the public consultation period of the PICO confirmation was that patients' fertility preservation is sometimes overlooked or de-prioritised when more critical healthcare is required. Consumers consider that not having to worry about paying for fertility preservation would mean avoiding an additional concern in a very stressful situation, and increase equity of access. However, some feedback noted that cryopreservation of ovarian tissue was experimental, invasive, and of uncertain fertility benefit.

8. Proposed intervention's place in clinical management

Description of Proposed Intervention
Ovarian tissue cryopreservation (OTC) is a method of fertility preservation in which a proportion or the whole ovary is surgically removed, usually by laparoscopy. In the laboratory, the ovary is dissected and the outer layer (ovarian cortex) which contains a large number of immature eggs is cut into small strips and frozen for future use.

When a patient has recovered from their diagnosis and wants to have a child, if they are unable to do this naturally, patients who have had OTC can have ovarian tissue transplantation (OTT) to enable a future pregnancy. This requires thawing and preparation of ovarian tissue for OTT which is performed after recovery from cancer (or non-malignant disease) and then re-implantation.

Description of Medical Condition(s)
The proposed patient population is defined by the requirement of gonadotoxic therapy. Specifically, the proposed population is females aged 0 to 40 years (pre pubertal and post pubertal) who are scheduled to undergo, or have completed gonadotoxic treatment. Gonadotoxic treatment includes any treatment which is associated with an intermediate or high risk of ovarian damage or sterility. This can include treatment such as chemotherapy, conditioning therapy for bone-marrow transplantation, pelvic surgery, or pelvic irradiation. Cancer is the primary group of diseases for which women are likely to undergo gonadotoxic treatment and would account for an estimated 78% of cases eligible for OTC. However there are some benign conditions that require this kind of treatment, such as autoimmune diseases, severe endometriosis and non-malignant haematological disorders, which would render patients eligible for the proposed service (an estimated 22% of patients).

The clinical management algorithm for current clinical practice and the proposed new service are shown in Figure 1 (shown in red), for patients who have not yet undergone gonadotoxic therapy.

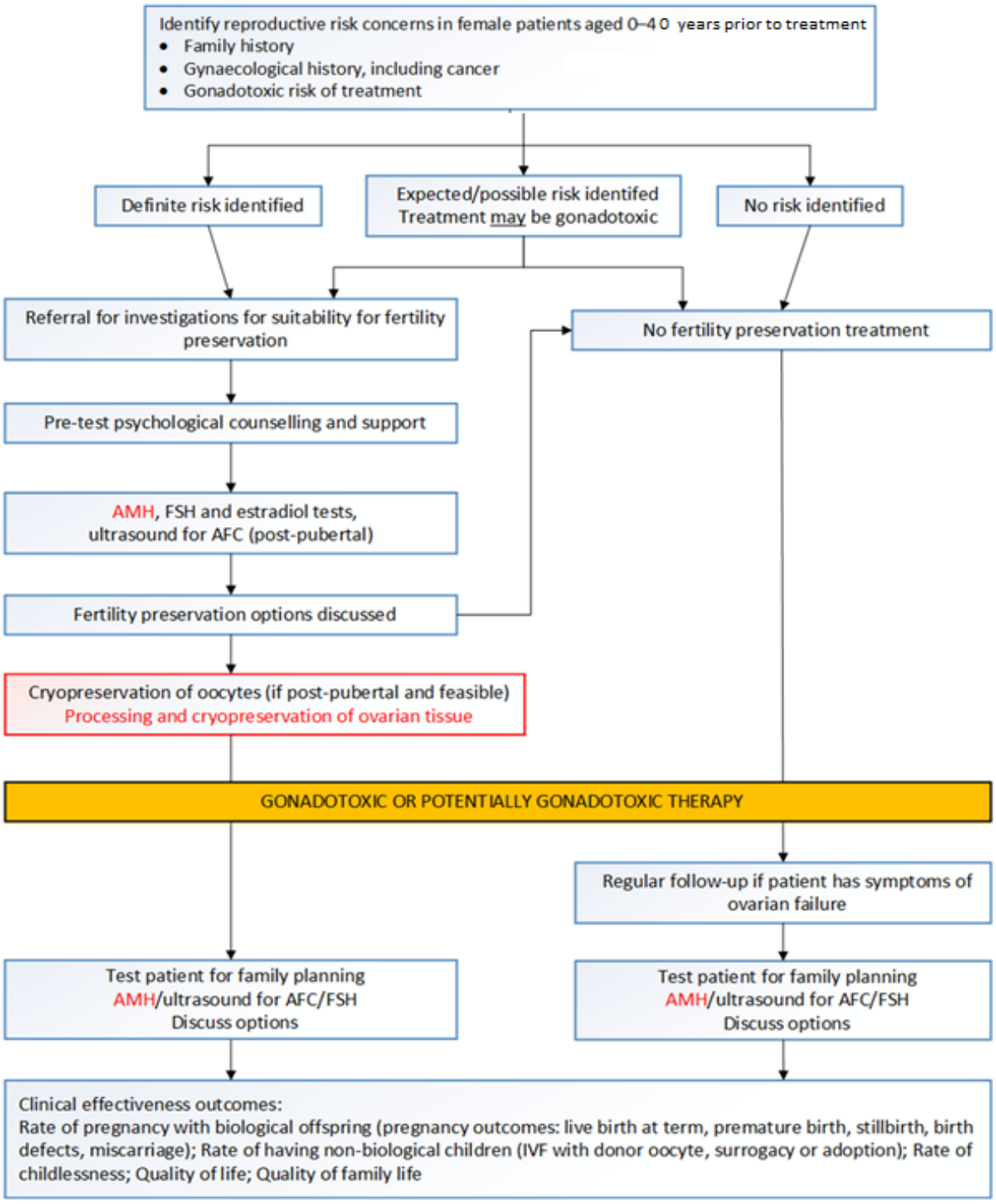

Figure 1 Current and proposed clinical management algorithm for the cryopreservation of ovarian tissue for female patients (aged 0-40 years) prior to receiving gonadotoxic treatment

AFC = antral follicle counts; AMH = Anti-Müllerian hormone; FSH = follicle stimulating hormone

In brief, females aged between 0 and 40 years are assessed for risk from treatment for cancer or non-malignant disorder, to their future fertility, and are triaged accordingly. Those who have a definite or possible risk will be referred for counselling and further testing.
For post-pubertal females, the proposed new service would be offered, following fertility assessment and counselling, as an alternative fertility preservation option alongside oocyte cryopreservation in the current clinical pathway.

The clinical management algorithm for current clinical practice and the proposed new service are shown in Figure 2 (shown in red), for patients who have already undergone gonadotoxic treatment.

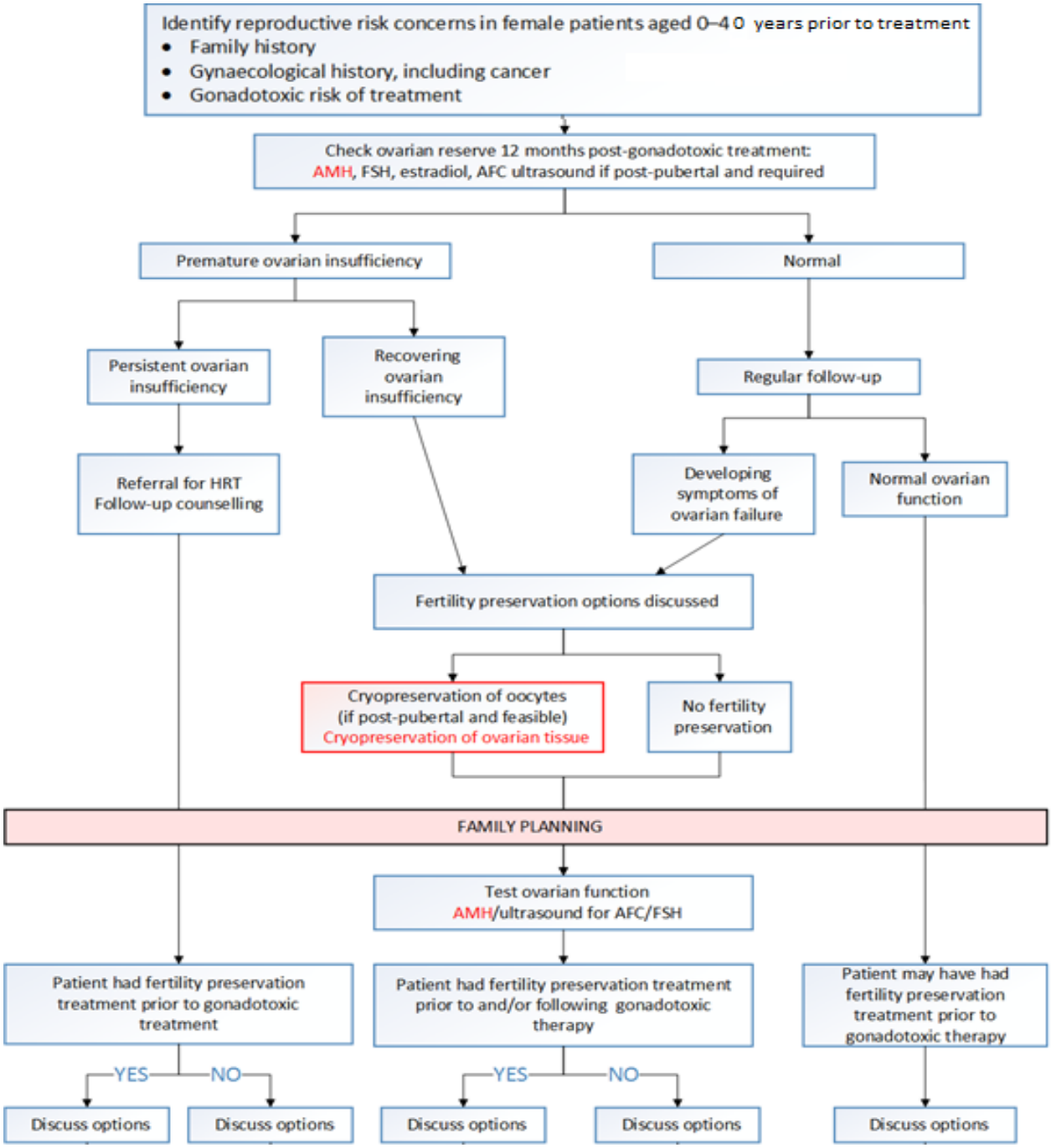

Figure 2 Current and proposed clinical management algorithm for cryopreservation of ovarian tissue for female patients (0–40 years) following completion of gonadotoxic treatment

AFC = antral follicle counts; AMH = Anti-Müllerian hormone; FSH = follicle stimulating hormone

In brief, fertility assessment would be conducted following treatment, with further testing recommended where there is a risk to future reproduction. Following counselling and discussion of preservation options, patients may choose to cryopreserve oocytes in current clinical practice if they are post-pubertal. In the proposed clinical pathway, both pre and post-pubertal patients may choose OTC, and post-pubertal patients may choose oocyte cryopreservation.

9. Comparator

The comparators described in the resubmission were listed separately for OTC and OTT (Table 2).

Table 2 Comparator details (as summarised in the Critique)

Comparator details OTC
Pre-pubertal patients: • No fertility preservation treatment • IVF with patient, donor gametes in adulthood • Childlessness Post-pubertal patients: • No fertility preservation treatment (which would be a key comparator for those unable to delay treatment long enough for a cycle of ovarian stimulation, or for those in whom ovarian stimulation is contraindicated) • IVF with patient, donor gametes in adulthood • Childlessness
Comparator details OTT
Pre-pubertal patients: • No fertility preservation Post-pubertal patients: • No OTT and no attempt at conception • No OTT and natural conception • Later OTT and natural conception • Later OTT and ART • No attempt at conception • Natural conception • ART • Childlessness

Source: Resubmission (MSAC Application 1435.1, pp.57-60)
ART=Assisted Reproductive TechnologyDAP=decision analytic protocol; NA=not applicable; OTC=ovarian tissue cryopreservation; OTT=ovarian tissue transplantation

The resubmission nominated no fertility preservation treatment as the main comparator because patients who have OTC are frequently unable to avail themselves of other options due to either being pre-pubertal at the time of their cancer diagnosis, being unwell, or having limited time before needing to start treatment.

The Critique stated this was reasonable for pre-pubertal patients who have no other fertility preservation options. However, post-pubertal females would be able to access other fertility preservation options such as oocyte cryopreservation (egg collection and storage) and embryo cryopreservation (fertilisation of an egg with either a partner's or donor sperm). Therefore, as recommended by the DAP, the resubmission should have nominated oocyte cryopreservation (egg collection and storage), embryo cryopreservation (fertilisation of an egg with either a partner's or donor sperm) and no fertility preservation treatment as relevant comparators.

10. Comparative safety

The application provided a narrative review of the literature; the Critique could not verify the literature search. Five additional studies were presented as evidence in the resubmission. The Critique assessed three of these five studies (Gellert et al. (2018); Diaz-Garcia et al. (2018); Rowell et al. (2019)), and excluded Gellert et al. (2018) as it was assessed at high risk of bias.

The Critique stated the main safety issues are consistent with those identified in the previous application. Specifically, one case series was identified which reported no surgical complications and no unanticipated treatment delays attributable to OTC in patients up to age 23. Signs of cell malignancy was found in 3.4% (2/59) of ovarian tissue samples tested.

11. Comparative effectiveness

The Critique stated that neither comparative safety, comparative effectiveness, nor the balance of clinical benefits and harms were presented in the resubmission. The Critique also reported that including the data from the previous application with additional data from Diaz-Garcia et al. (2018), which reported an uptake rate of 6.2% (50/800; 44 seeking pregnancy and 6 for endocrine purposes), gives a combined uptake rate of 4% (215/5418). Mean storage time in the Diaz-Garcia study was 5.5 years in the OTC/OTT cohort.

The Critique stated that data on storage discontinuation rates, long-term safety for mothers and babies, or the quality of life impact of repeated storage decisions were not presented in the resubmission or identified in the new evidence.

The Critique stated that no new studies were identified which directly addressed the risk that stored ovarian tissue will contain malignant cells that could be transplanted back in to the patient during OTT. The Applicant provided a description of the steps taken to test for and rule out malignancies. The Critique stated it was unclear whether the description is based on best practice or expert consensus, as no citations were provided. The description includes xenograft testing for patients with a leukaemic or ovarian cancer diagnosis. It was unclear whether this would require additional accreditation or laboratory facilities. In addition, xenograft testing does not have an MBS listing, so this may be an additional cost to the patient. The Critique stated that the main effectiveness issues are consistent with those identified in the previous application; however, there was now (low quality) comparative evidence for pregnancy and live birth rates (Table 3).

Table 3 Balance of clinical benefits and harms of OTC, relative to oocyte cryopreservation (or no comparator), for all patients

Outcomes (units)	Participants (studies)	Quality of evidence (GRADE)[a]	Relative I)	Risk with oocyte preservation	Risk with OTC	Comments
Live birth rate	*K = 1 (Diaz-Garcia 2018, prospective cohort)* *N=1824*	⊕⊕⊙⊙	*145 less per 1000 patients (-319, 29))*	*16/49 (32.7%)*	*8/44 (18.2%)*	-
Pregnancy Rate	*K = 1 (Diaz-Garcia 2018, prospective cohort)* *N=1824*	⊕⊕⊙⊙	*135 less per 1000 patients (-326, 55))*	*20/49 (40.8%)*	*12/44 (27.3%)*	*7 patients conceived spontaneously following OTT.*
Complications of OTC	*K = 1 (Rowell 2019, case series)* *N = 64*	⊕⊙⊙⊙	*NA*	*NA*	*0/64*	*Data from case series of patients who had OTC (no control group). No patients underwent OTT*
Proportion of tissue with cell malignancy	*K = 1 (Rowell 2019, case series)* *N = 64*	⊕⊙⊙⊙	*NA*	*NA*	*2/59 (3.4%)*	*No patients underwent OTT*

Source: Critique; Compiled during evaluation CI=confidence interval; OTC=ovarian tissue cryopreservation
a GRADE Working Group grades of evidence (Guyatt et al.., 2013)
⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.
⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Clinical Claim

The Critique stated that after consideration of the limited additional comparative evidence, and the lack of power in the prospective cohort study by Diaz-Garcia et al., the previous clinical claims of uncertain clinical effectiveness and non-inferior safety remain unchanged.

The Critique stated that the application's implicit claim was that greater access to OTC and OTT would increase rates of live births. The applicants assert that as of 2018, there have been over 140 live births reported following OTC and OTT, though the number of patients who have undergone OTC and OTT is not known.

12. Economic evaluation

The resubmission did not present an economic evaluation. The Critique stated that a cost-effectiveness analysis (i.e. incremental cost per extra live birth as requested by MSAC) would be possible as comparative data is now available (albeit the quality of evidence is low), though probably inappropriate as OTC and OTT would likely be dominated by oocyte cryopreservation, given the high cost of OTC and OTT and the clinical evidence.

13. Financial/budgetary impacts

The resubmission did not provide an estimate of financial implications of OTC and OTT. However, financial estimates were provided by the Critique using an epidemiological approach (as recommended by the MSAC in the PSD) to estimate the financial implications of the introduction of OTC and OTT (Table 4). The Critique used the 75% rebate with the assumption that all proposed services would be claimed as part of hospital episode.

Table 4 Total costs to the MBS associated with OTC and OTT

	2019-20	***2020-21***	***2021-22***	***2022-23***	***2023-24***
OTC					
Number of services	*529*	*603*	*688*	*784*	*894*
Sub-total cost	*$258,834*	*$295,070*	*$336,380*	*$383,474*	*$437,160*
OTT					
Number of services	*18*	*21*	*24*	*27*	*31*
Sub-total cost	*$8,560*	*$9,758*	*$11,124*	*$12,681*	*$14,457*
Co-administered services currently MBS listed - MBS items 35638, 20706 and 51303					
Number of services	*83*	*95*	*108*	*124*	*141*
Sub-total cost	*$62,063*	*$70,752*	*$80,657*	*$91,949*	*$104,822*
Total cost to MBS	***$329,456***	***$375,580***	***$428,161***	***$488,104***	***$556,439***

Source: Compiled during evaluation
OTC=ovarian tissue cryopreservation; OTT=ovarian tissue transplantation

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Changes to item descriptor	Consider if PASC should review whether OTT thawing/processing should be included as additional new item number Seek explanation from applicant as to why there was a change in age group and proposed fee. Exclude OTC in patients with ovarian cancer/leukaemia (as per pre-ESC reply).
Changes to comparators	PASC did not see this resubmission; determine whether the changes to comparators are significant enough to warrant a complete review by PASC.
There is still no evidence to support use in pre-pubertal girls	Resubmission could define 1) pre-pubertal vs 2) post-pubertal/adult, and may wish to focus on both or just one group, given that there will not be any evidence in the pre-pubertal group for 20 years and the literature still considers it to be an experimental procedure in this group.
Advice provided to applicant for future resubmission	The applicant did not follow the template. Future resubmission advice should be clear to applicant.
Malignancy protocol	Clarify in future resubmission if the 4 provided malignancy protocols (including xenograft testing) are a standard protocol around Australia, or by expert consensus as no references provided
Evidence on comparative effectiveness is still limited and uncertain	Suggest that next resubmission includes mature data from the Australasian Oncofertility Registry.
No cost-effectiveness analysis was presented and cost analysis presented is not useful to inform funding decisions	MSAC concerns have not been addressed, but without more evidence no further economic analyses can be done.
Large costs to patients, e.g. storage, test for malignancies, etc. (unlikely to improve access)	Significant out-of-pocket costs is an equity issue.
No new data were identified regarding the lifetime costs of storage	May need to wait for data to become available from the Australasian Oncofertility Registry.
Uncertain financial estimates	Costs to MBS are sensitive to estimated use of OTC, which is uncertain.

ESC Discussion

Application 1435.1 requests the creation of multiple Medicare Benefits Schedule (MBS) items for processing and cryopreservation of ovarian tissue (OTC), as well as thawing and preparing ovarian tissue for ovarian tissue transplantation (OTT) following gonadotoxic treatment. OTC is the only option for females immediately before gonadotoxic treatment, pre-pubertal girls (with no mature oocytes), or when risk of infertility is high (in association with mature oocyte preservation).

ESC noted that the applicant provided a narrative rather than following the template (i.e. there were no sections A to F) and considered that perhaps the applicant was not familiar with the resubmission process. In particular, no clinical claim was discussed, and there was no additional evidence on comparative safety and limited additional evidence on comparative effectiveness.

ESC noted changes in the proposed MBS item descriptors compared to those in the original application. The two items for cryopreservation differ in the age restriction (changed from females <45 years old to <40 years old for both items) and fees proposed (changed from $800 to $608.64 in Item 1 and from $1200 to $944.82 in Item 2). No justification was provided for either change, although ESC considered that the change in age may be related to risks associated with, or chance of successful pregnancy from in vitro fertilisation.

ESC noted that a third item was added to the resubmission for thawing and preparing ovarian tissue for transplantation, because the primary outcomes of the OTC application (pregnancy and live births or other pregnancy outcomes) requires OTT to follow OTC.

ESC noted that the resubmission nominated no fertility preservation treatment as the main comparator. While this is reasonable for pre-pubertal patients who have no other fertility preservation options, post-pubertal females should be able to access other fertility preservation options such as oocyte or embryo cryopreservation. No information was provided on the proportion of post-pubertal females that would be unable to access these options. ESC noted that if the comparator is being changed then the application should be reviewed by PASC.

Alternatively, MSAC may wish to consider whether the patient restriction in the item descriptor should be amended to include only females who have no other appropriate fertility preservation options.

ESC noted that no new studies of long-term safety for mothers and babies were identified since the original contracted assessment. ESC agreed with the applicant that it will take 20 years to attain long-term safety data for OTC in pre-pubertal girls.

ESC noted that even with new evidence, data on the number of live births after OTC in post-pubertal females remain limited, and the uptake of OTT is estimated at around 4%. The applicants assert that as of 2018, there have been over 140 live births reported following OTC and OTT; however, the number of patients who have undergone OTC and OTT is not known.

ESC noted that in the pre-ESC response, the applicant stated that they do not use OTC in patients with leukaemia or ovarian cancer. ESC queried whether this should be reflected in the item descriptor.

ESC noted that no new data were identified regarding the lifetime costs of storage. One study comparing oocyte cryopreservation (OC) with OTC/OTT reported a mean storage time of 3.9 years in the OC cohort compared with 5.5 years in the OTC/OTT cohort. ESC noted that legislation regarding the length of time that gametes may be stored for varies from state to state, but is most commonly 10 years.

ESC noted MSAC's request that the applicant determine the quality of life (QoL) impact on women of repeated decisions about whether to continue tissue storage, and storage costs. The resubmission did not address this as they were not pursuing this to be included in the MBS item listing. ESC noted that it is difficult to find evidence on the QoL impact of storage. ESC also queried why MSAC requested this information, because this type of specific storage issues (i.e. QoL) have not been queried in previous applications relating to male/female assisted reproductive technology.

ESC noted the applicant's statement that 'ovarian tissue cryopreservation is an acknowledged fertility preservation technique and is no longer considered experimental'. However, ESC

considered that the literature referenced suggests the technique is still considered experimental in pre-pubertal girls.

ESC noted that MSAC requested a cost-effectiveness analysis, such as incremental cost per extra live birth. However, due to lack of evidence on comparative effectiveness, no economic evaluation was provided. However, it was noted a cost analysis was provided in the original Application 1435. ESC considered that the cost analysis (previously seen by MSAC in March 2018 Meeting) did appear to capture all the relevant costs; however, ESC noted that a cost analysis is not useful for decision-making purposes.

ESC noted that the applicant suggests using MBS item 35638 (complicated operative laparoscopy) in combination with MBS item 14203 (hormone or living tissue implantation) for OTT. ESC queried whether item 35638 may need rewording (to include OTT). ESC also queried whether the fee would be the same for heterotopic (transferred into a different location) or orthotopic (placed into its original location) transplantation. ESC also noted that surgical assistance (MBS item 51303) and anaesthesia (MBS item 20706) would be required.

ESC noted that the costs to the MBS are sensitive to the estimated uptake of OTC. The number of eligible patients may be greater than estimated, as the proportion of incident cases of cancer undergoing gonadotoxic treatment is uncertain. The applicants suggest that this proportion could be as high as 80% (base case 50%), which would increase estimated costs to the MBS from $560,000 to $890,000 in the fifth year. ESC noted that there will also be increases in co-claimed items: laparoscopy, surgical assistance and anaesthesia (for both OTC and OTT).

ESC noted that for an individual patient, OTT may happen years (or even decades) after the OTC services are performed. This makes it difficult to estimate the financial impact of OTT on the MBS. The key factor is the uptake rate of OTT following OTC, which the published literature suggests is very low.

ESC noted that there are significant out-of-pocket costs associated with both OTC and OTT, which may become an equity issue.

ESC noted that there is now an Australasian Oncofertility Registry and suggested that the applicant may want to use data from the registry to seek evidence in the future.

15. Other significant factors

Nil.

16. Applicant's comments on MSAC's Public Summary Document

The applicants are very concerned that MSAC have not supported this application and we summarize the reasons why this needs to be urgently reviewed. Ovarian Cryopreservation is no longer considered experimental despite MSAC questioning this. The American Society of Reproductive Medicine (ASRM) is the leading American professional society of reproductive medicine specialists, scientists and ethicists providing national and international advice about reproductive care. This month the ASRM released their paper 'Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion' in 'Fertility and Sterility'[1]. This report was developed by the Practice Committee of the ASRM and the Society for Reproductive Endocrinology and Infertility (SREI), it represents the highest level

[1] DOI: https://doi.org/10.1016/j.fertnstert.2013.08.012

of guidance on international evidence based practice. The report makes key recommendations in line with our application 1435:

1. Ovarian tissue banking is an acceptable fertility-preservation technique and is no longer considered experimental;
2. Ovarian tissue banking is the only method to preserve fertility for pre-pubertal girls since ovarian stimulation and IVF are not options. Working with these individuals and their parents requires an approach that is sensitive to various levels of physical and psychological development. Close collaboration among clinicians is required and careful counseling and informed consent are especially recommended;
3. This technique has been proposed principally for pre-pubertal females and for those who cannot delay cancer treatment in order to undergo ovarian stimulation and oocyte retrieval;
4. This technique has been successful in patients with a variety of malignant and nonmalignant conditions facing gonadotoxic therapies;
5. Given the current body of literature, ovarian tissue cryopreservation should be considered an established medical procedure with limited effectiveness that should be offered to carefully selected patients which we have proposed in our application;
6. Ovarian tissue transplantation can be technically challenging and should be offered only by centers with the necessary laboratory and surgical expertise.

In Europe the equivalent leading organisation is the European Society of Human Reproductive and Embryology (ESHRE) and they are also updating their recommendations. ESHRE will publish their new guidelines early next year. These will mirror the statements made by ASRM.

In keeping with these recommendations, a number of countries have already received government funding for universal public or insurance provisions of OTC including Austria, Belgium, Israel, Italy, Finland, Germany, NHS Scotland, Norway, Sweden, Switzerland, The United States of America. NHS England are correctly in the final stages of approval.

Malignant Transformation - There is a legitimate concern regarding the potential for reseeding tumor cells following ovarian tissue cryopreservation and transplantation procedures in cancer patients and hence very robust protocols for prevention of re-seeding are followed. These are detailed in the application and supported by international practice. So far no cases of recurrence of cancer following ovarian tissue grafting have been reported in the World literature despite intensive surveillance over many hundreds of procedures. Although many types of cancer virtually never metastasize to the ovaries, leukemias are systemic in nature and therefore pose a risk. Therefore, autologous transplantation is contraindicated in situations where cancer cells may be present in cryopreserved ovarian tissue. In these cases, in-vitro methods of removing ovarian follicles for IVF are undertaken (IVM). This results in later transfer of only the egg cell itself, in the absence of any blood derived cells and hence there is no possibility of re-seeding the leukemic cells. IVM for this purpose is outside the remit of our application but is mentioned here as an option for those patients for whom it is not safe to undertake ovarian tissue freezing and re-grafting.

The Australian protocol discussed in our application gives clear methods for mitigating the risk of malignant contamination and methods for detection of contamination are used which are tumour specific. No patient will have a tissue transplant if there is evidence of residual disease. The ongoing collection of data on the Australasian Oncofertility Registry will provide additional reassurance, with no cases being reported to date. It will never be possible to perform a randomized trial in this area of practice, given the extremely long latency between tissue collection and re-grafting and the huge implications to patients if they are

randomized not to receive a tissue collection procedure. Patients would simply decline to enter such a trial. We believe that there is more than sufficient evidence of safety from registries in the USA and Europe to provide reassurance to patients, their relatives and families and to regulators that ovarian tissue collection and re-grafting is a safe and no longer experimental procedure.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website