



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1435 - Processing and cryopreservation of male and female gonadal tissue and gametes prior to or after gonadotoxic treatment to preserve fertility for the future (Part A)

Applicant: Kids Cancer Centre, Sydney Children's Hospital

Date of MSAC consideration: MSAC 71st Meeting, 23 November 2017

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

An application was received from the Kids Cancer Centre requesting two new Medicare Benefits Schedule (MBS) listings for:

- Processing and handling of semen in preparation for cryostorage as part of fertility preservation treatment for male patients who have or will receive gonadotoxic treatment, and
- Processing and handling of testicular tissue in preparation for cryostorage as part of fertility preservation treatment for male patients who have or will receive gonadotoxic treatment.

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 supported MBS funding for the processing, analysis and cryopreservation (freezing) of semen to preserve fertility in post-pubertal males undergoing gonadotoxic (radiation or chemotherapy) treatment. MSAC advised that cryopreservation of semen has non-inferior safety with superior effectiveness and is probably cost-effective with storage costs removed from the economic modelling.

MSAC advised that the MBS item descriptor should be limited to semen collection, post-pubertal males in Tanner stages II–V, with specialist referral only and a maximum of two semen collection cycles.

MSAC did not support MBS funding for testicular tissue biopsy, processing and cryopreservation in pre-pubertal children undergoing gonadotoxic treatment due to its inferior safety profile and uncertain clinical effectiveness and cost-effectiveness compared with standard care.

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

MSAC noted that the application considered is Part A of MSAC application 1435. Part B of this application relates to processing and cryopreservation of ovarian tissue prior to or after gonadotoxic treatment to preserve future fertility, which will be considered by MSAC in March 2018.

MSAC noted that there were two populations included in Application 1435 Part A:

1. processing and cryopreservation of semen or testicular tissue in post-pubertal males (adolescents and adults) undergoing gonadotoxic treatment (population 1); and
2. testicular tissue biopsy, processing and cryopreservation in pre-pubertal children undergoing gonadotoxic treatment in the hope that future technology may allow the re-implantation of the tissue or spermatogonial stem cells (population 2).

MSAC agreed that use of the service in population 2 is currently considered experimental, is invasive and of uncertain clinical benefit. MSAC noted that there is currently no outcome data in this population. MSAC noted that processing and cryopreservation of testicular tissue in post-pubertal males was also considered experimental and that no evidence was available with respect to using the procedure for these patients. MSAC agreed that a resubmission for these populations should be considered by ESC and MSAC once evidence becomes available.

MSAC acknowledged the clinical need for fertility preservation in patients undergoing gonadotoxic treatment and the ethical need to ensure equitable access to fertility preservation.

MSAC noted that overall the evidence suggests that cryopreservation of sperm has non-inferior safety and superior effectiveness to standard care (no fertility preservation). MSAC noted that the evidence from the 13 observational studies presented indicates that having a cryopreserved sperm sample doubles the chances that an azoospermic or aspermic male (due to gonadotoxic treatment) will be able to have a biological child compared to the use of invasive procedures to extract sperm post-treatment. MSAC noted that the evidence suggests that 20 males would need to cryopreserve sperm in order for one additional man to become a biological father.

MSAC noted that cost-effectiveness was presented in terms of the cost per additional male (or couple) achieving parenthood, the cost per additional live birth and the cost per additional parent- quality-adjusted life year (QALY) gained. MSAC recalled that the cost per additional live birth is the measure previously accepted as appropriate by MSAC for this type of outcome. MSAC advised that the department should ensure that equivalent metrics are used for Application 1435 Part B for consistency. MSAC noted that willingness to pay for a live birth, averaged across the population, may also be informative in assessing the cost-effectiveness of this type of intervention.

MSAC noted ESC's comments that storage costs should be separate from collection and processing as the cost of storage should not be covered by the MBS. MSAC agreed that it was not appropriate for storage costs to be included in the item fee and advised that the requested fee should be reduced by the cost of the storage component currently included.

MSAC noted that the economic modeling presented involved a level of uncertainty due to the inclusion of storage costs, and the clinical benefits and utilisation rates of cryopreserved sperm are uncertain as they are based on outcomes from relatively small observational studies. MSAC noted that the base case incremental cost-effectiveness ratios (ICERs) for all post-pubescent males aged <60 were approximately \$366,000 per additional parent QALY or \$79,000 per additional live birth. The ICERs were significantly higher for males who are adolescent at diagnosis at approximately \$1.2 million per parent QALY or approximately

\$297,000 per additional live birth. MSAC noted sensitivity analyses that showed that when storage costs are decreased to \$100 per year the cost per additional live birth decreases from approximately \$79,000 to less than \$40,000. Overall MSAC considered that once storage costs are removed, the proposed service is likely to have acceptable cost-effectiveness.

MSAC noted that the estimated uptake of the service is high and that the estimates do not include indirect financial impacts to the MBS from additional services such as assisted reproductive technology services.

MSAC noted that some of the ethical issues raised are addressed by NHMRC guidelines and state laws. MSAC were concerned that there are still unresolved ethical issues associated with the proposed service, particularly in terms of the legal responsibilities and the responsibility for the cost of ongoing storage for patients and parents as children who have cryopreserved become adults. However, MSAC concluded that it is not within the Committee's remit to address these ethical issues.

MSAC noted that access to counselling for patients undergoing fertility preservation is an unresolved issue. However, patients are able to access publicly funded psychological support services under existing MBS and non-MBS arrangements

In considering the appropriate minimum age limit for the proposed service MSAC acknowledged that there is variation in both endocrine and emotional maturity that should be taken into consideration for the proposed service. MSAC advised that the item descriptor should specify the service is limited to boys at Tanner II stage or above for puberty.

MSAC noted that the item should require specialist referral and that the limit on the number of cycles should be included in the descriptor, as recommended by ESC. MSAC advised categorisation of the procedure as a Type C procedure (out-of-hospital procedures which do not normally require hospital accommodation/admission) would be appropriate.

MSAC noted consumer support for access to this service and concern regarding the potential out-of-pocket costs for ongoing storage of samples.

4. Background

MSAC has not previously considered processing and cryopreservation of male and female gonadal tissue and gametes prior to or after gonadotoxic treatment to preserve fertility for the future.

The protocol for Application 1435 included the processing and cryopreservation of male and female gonadal tissue and gametes prior to or after gonadotoxic treatment to preserve future fertility. For the purposes of the evaluation by ESC and MSAC, Application 1435 has been split into two parts:

- Application 1435 – PART A seeks to establish MBS listing of processing and cryopreservation of semen, sperm and testicular tissue prior to or after gonadotoxic treatment to preserve future fertility; and
- Application 1435 – PART B seeks to establish MBS listing of processing and cryopreservation of ovarian tissue prior to or after gonadotoxic treatment to preserve future fertility. Application 1435 – PART B is scheduled to be considered by ESC in February 2018, together with Application 1434 Anti-Müllerian hormone test, as the services are linked.

5. Prerequisites to implementation of any funding advice

As at May 2017, there are 94 different IVF components listed on the ARTG, which would be relevant to this application. Those identifiable as being related to cryopreservation of sperm are shown in Table 1. No ARTG listings were identified specific to cryopreservation of testicular tissue.

Table 1 Sperm cryopreservation items listed on the ARTG

ARTG no.	Product description	Product category	Sponsor
151269	Quinn's Advantage Sperm Freeze – In vitro fertilization culture medium	Device	Origio Australia Pty Ltd
161619	CryoSperm - In vitro fertilization culture medium kit	Device	Origio Australia Pty Ltd
132761	Sydney IVF Sperm Cryopreservation Buffer (K-SISC) – In vitro fertilization culture medium kit	Device	William A Cook Australia Pty Ltd

Source: Therapeutic Goods Administration, accessed 10th May 2017 [Link to TGA.gov.au](http://www.tga.gov.au)

All fertility and andrology centres are licensed by the Reproductive Technology Accreditation Committee (RTAC) Certification Scheme. All processes, from clinics to laboratories and day hospitals, will have accreditation.

Semen analysis and related testing (sperm antibodies etc) are covered by Medicare but sperm cryostorage is currently not specified in the National Association of Testing Authorities (NATA) accreditation.

6. Proposal for public funding

The proposal is for new MBS item numbers to cover the processing and freezing components of cryopreservation. The proposed item descriptors are summarised in Table 2. These items are not intended for use where fertility preservation is for reasons that are non-medically related.

Table 2 Proposed MBS item descriptors for processing and cryopreservation of testicular tissue and sperm

Category 3 – Therapeutic Procedures
<p>Proposed item 1</p> <p>Processing and cryopreservation of testicular tissue for fertility preservation treatment before or after completion of gonadotoxic treatment for malignant or non-malignant conditions, in males up to 60 years old.</p> <p>This item is only for use when a semen sample is unable to be produced.</p> <p>Fee proposal: Cost \$675</p> <p>Explanatory notes:</p> <ul style="list-style-type: none"> • This Medicare item number should be used with Medicare item numbers 37605 and 37606 for surgical collection of testicular tissue.
<p>Proposed item 2</p> <p>Processing and cryopreservation of semen for fertility preservation treatment before or after completion of gonadotoxic treatment for malignant or non-malignant conditions, in males up to 60 years old.</p> <p>Fee proposal: Cost \$495</p> <p>Explanatory notes:</p> <p>Maximum of two semen collection cycles, one cycle collected prior to a patient undergoing the first cytotoxic/radiation treatment and the second cycle to be collected if the patient has relapsed and requires treatment.</p> <p>A semen cycle collection process involves obtaining up to 3 semen samples on alternate days producing up to 50 cryopreserved straws of frozen sperm (a cycle is considered to be a set of semen samples collected over a few days ahead of a treatment).</p>

In its pre-MSAC response, the applicant agreed with ESC that the definition of semen cycles should be included in the item descriptor. The applicant defined a semen cycle as a collection of up to three collections.

The applicant also stated preference to not to include a minimum lower age limit for boys having semen collections. The assessment of suitability is dependent on history and physical examination based on a Tanner Staging to confirm pubertal onset. It would be more accurate and inclusive to use the eligibility term to be ‘patients who have entered puberty’ and not include an age. If an age should be included, then the applicant believes it should be set at ten years of age so as to include those boys in early puberty at the time of a cancer diagnosis.

7. Summary of Public Consultation Feedback/Consumer Issues

The department received 88 responses from public consultation from a range of organisations and key bodies. Key issues that were raised in the consultation feedback and policy impact were:

- the majority of responses were in strong support of the proposed services being publicly funded. Themes that were repeated included that patients should have a choice and the right to have children in the future; reducing financial burden; and equity of access.
- a number of responses differentiated between processing of semen, and processing of ovarian or testicular tissue. Feedback described processing of semen as a long established, minimally invasive and proven method for preserving fertility that may result in a live birth. In contrast, some feedback noted processing of ovarian or testicular tissue to be experimental, invasive, and of uncertain future fertility benefit.
- one feedback response noted that in figures 4b and 5b (clinical algorithms), the term “semen morphology” is incorrect and should become “semen analysis”.
- one feedback response noted that comparators could also include IVF procedures using donors, surrogates or adoption in terms of having a family.

8. Proposed intervention’s place in clinical management

The proposed intervention is the processing and cryopreservation (freezing) of male gonadal tissue or gametes, which include semen, sperm or testicular tissue.

The aim of the cryopreservation is to preserve fertility, prior to undergoing, or after completion of, gonadotoxic treatment. Cryopreservation of semen and sperm is well established, and considered best practice for individuals who may lose fertility due to treatments for malignancies or non-malignant conditions.

Cryopreservation of semen, sperm or testicular tissue prior to gonadotoxic treatment will offer men, who are azoospermic after gonadotoxic treatment, the option to potentially father a child.

Figure 1 shows the clinical management algorithm for males who are undergoing gonadotoxic treatment, and have the option of fertility preservation treatments prior to treatment.

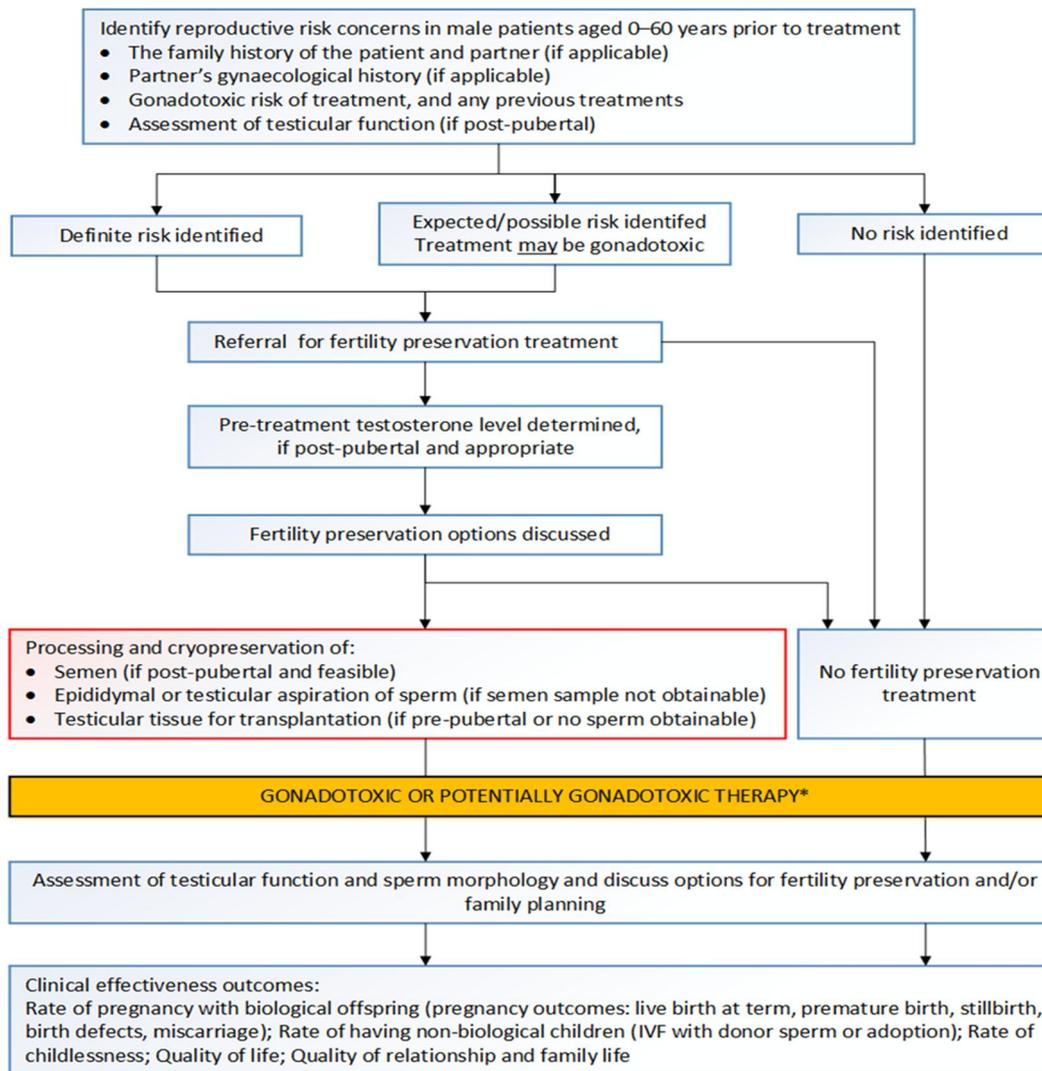


Figure 1 Clinical management algorithm for processing and cryopreservation of semen or testicular tissue prior to gonadotoxic treatment (red box for proposed MBS items)

9. Comparator

Currently there are no other methods for processing and cryopreserving semen, sperm and testicular tissue, therefore the comparator is standard care.

For men who do not wish to father children, or are able to conceive naturally after gonadotoxic treatment, the absence of a cryopreserved sample will have no impact. However, for those who are azoospermic or unable to ejaculate following treatment and wish to father children, the options include attempting to retrieve a sperm sample using techniques such as microdissection testicular sperm extraction (mTESE) or EEJ.

10. Comparative safety

For the majority of males scheduled to undergo gonadotoxic treatment, producing a sperm sample is non-invasive and relatively easy. The majority of post-pubertal males (approximately 94%) are able to masturbate, and have sperm in their ejaculate, producing a sperm sample in a safe way, which can then be cryopreserved. However, techniques used to extract testicular tissue or sperm from the testicles or epididymis in those who are pre-pubertal, azoospermic, or unable to ejaculate, are invasive and require anaesthesia, and

therefore have risks associated with them. Likewise, re-implantation of testicular tissue has theoretical risks involved.

Processing and cryopreservation of sperm and testicular tissue occurs outside the body, and poses no harm to the patient.

11. Comparative effectiveness

Pre-pubertal boys

There is no evidence of testicular tissue biopsies being effective at helping survivors of childhood cancer have children. However, the procedure is being offered to many patients due to the potential that re-implantation of testicular tissue or spermatogonial stem cells will be able to restore fertility to survivors of childhood cancer in the near future.

While pre-pubertal boys do not have any sperm, the majority of peri-pubertal boys who underwent a testicular tissue biopsy had spermatogonia extracted.

The summary of findings from the literature concerning cryopreservation of testicular tissue in pre-pubertal boys, is shown in Table 3.

Table 3 Balance of clinical benefits and harms of testicular tissue cryopreservation in pre-pubertal males, as measured by the critical patient-relevant outcomes

Outcome	Participants (studies)	Quality of evidence (GRADE) ^a	Results	Interpretation
Harms of testicular tissue biopsy	K=4 case series N=123	⊕⊖⊖⊖	1/123 (0.8%) adverse event rate 1 case of post-operative scrotal cellulitis in a 17-month old patient	Testicular tissue biopsies are invasive procedures, involving anaesthesia. However, they have a low rate of complications.
Achieving paternity	K=0	N/A	-	There is no evidence at this time that re-implantation of testicular tissue or spermatogonial stem cells improves fertility.
Quality of life	K=0	N/A	-	-

On the basis of the evidence profile, the assessment suggested that, relative to no cryopreservation, cryopreservation of testicular tissue in pre-pubertal boys has inferior safety and uncertain effectiveness.

Post-pubertal adolescents and men

Four cohort studies combined to show a trend that those men who cryopreserved sperm were more likely to become fathers, than those who did not (n=1859, RR=1.29, 95%CI 0.93, 1.79). However, the rate of fatherhood in those men who cryopreserved sperm samples as compared to those who did, was confounded by the fact that those who were interested in becoming fathers, were more likely to cryopreserve their sperm.

There was a trend favouring the use of fresh sperm, collected post-gonadotoxic treatment, rather than cryopreserved sperm, for pregnancy rates (k=4, n=151, RR=0.73, 95%CI 0.45, 1.19), but there was no difference in paternity rates (k=5, n=195, RR=1.17, 95%CI 0.51, 2.70).

Therefore, if men are able to produce sperm after gonadotoxic treatment, their chances of fathering a child are the same with or without the use of cryopreserved sperm. However, the key benefit of having cryopreserved sperm is so that it can be used if the male cannot produce sperm after gonadotoxic treatment. Clinicians are unable to predict which patients will be infertile following gonadotoxic treatment. The mean proportion of males in the studies included in the systematic review, who became azoospermic after gonadotoxic treatment, was 34.5%. However, the evidence suggests that only 10% of men actually used their cryopreserved sample.

The best method of determining the effectiveness of cryopreservation is to compare the success rate of ART using cryopreserved sperm, with the success rate of extracting sperm post-treatment by means of TESE or EEJ, and using those sperm for ART. A summary of case series data showing the number of deliveries per couple, who used a particular sperm retrieval approach, is shown in Table 4. Those couples who underwent ART using cryopreserved sperm were over twice as likely to have a live birth than those who relied on TESE post-treatment. For approximately half of the azoospermic patients and a small proportion of other patients with impaired fertility, cryopreservation of sperm prior to treatment may be their only chance of having biological children.

Table 4 Indirect comparison of fatherhood success rate per couple undergoing ICSI who attempted to use sperm retrieved by TESE after gonadotoxic treatment compared to those who attempted to use their sperm cryopreserved prior to treatment

ICSI outcomes	Pre-treatment	Post-treatment	
	Cryopreserved sperm	TESE – frozen sperm	TESE – fresh sperm
Proportion of couples who attempted ART who had a delivery	k=13	k=5	k=3
Median (range)	54% (20–100%)	19% (8–40%)	20% (10–35%)
Mean (95%CI)	48% (39, 56)	22% (12, 32)	22% (4, 40)

CI = confidence interval; ICSI = intracytoplasmic sperm injection; k = number of studies; TESE = testicular sperm extraction

Only one in ten patients who cryopreserved a sperm sample tried to use it for ART. Of these, half were successful at achieving paternity.

Quality of life was impaired in men who wanted children but were not able to have any, compared to those who had achieved paternity (using the EORTC QLQ-C30 and TC mode EORTC QLQ-TC26 questionnaire) (Stoehr et al. 2013). However, the financial impact of cancer was considered greater among survivors who achieved paternity, when compared to those who did not achieve paternity (Stoehr et al. 2013).

Men who banked their sperm were found to better handle their decisions and feelings about the cancer and/or its treatment and the possible consequences (as determined using the EORTC QLQ-C30) (Pacey, A et al. 2013).

The summary of findings for cryopreservation of sperm is shown in Table 5.

Table 5 Balance of clinical benefits and harms of semen or sperm cryopreservation in post-pubertal males, relative to no cryopreservation, and TESE or EEJ, as measured by the critical patient-relevant outcomes in the key studies

Outcome	Participants (studies)	Quality of evidence (GRADE) ^a	Results	Interpretation
Harms	k=0 for safety of masturbation k=5, n=86 for safety of TESE k=2, n=71 for safety of EEJ	⊕⊖⊖⊖ naïve indirect comparison	Producing a sperm sample by masturbation is very safe, although can be embarrassing for adolescents. 1 complication from EEJ (4.3%), with patient having pulmonary aspiration during induction of anaesthesia, which resulted in pneumonia. No complications reported due to TESE.	Extracting a sample by EEJ or TESE has theoretical risks, as they are invasive procedures and require anaesthesia, but the risks are minimal. Cryopreserving a sperm sample is likely to be safer than undergoing an invasive procedure post-gonadotoxic treatment, for those who become azoospermic or unable to ejaculate.
Achieving paternity (by natural conception or ART)	k=4 cohort studies; n=1859 Comparison of paternity in those who cryopreserved sperm, vs those who did not	⊕⊖⊖⊖ confounded and heterogeneous	RR=1.29 (95%CI 0.93, 1.79) Those who cryopreserved sperm were more likely to have at least one child compared to those who did not cryopreserve sperm	Those who want children are more likely to cryopreserve sperm. These results therefore do not address the effectiveness of the technology. A more informative comparison would be achieving paternity from cryopreservation as compared to other methods for achieving paternity.
Achieving paternity (using ART, for those unable to conceive naturally)	k=13 case series for pre-treatment cryopreservation k=3 case series for TESE post-treatment	⊕⊖⊖⊖ naïve indirect comparison	Paternity achieved in median 54% of those who used cryopreserved sperm obtained prior to gonadotoxic treatment Paternity achieved in median 20% of those who used TESE post-gonadotoxic treatment	In those men who are unable to conceive naturally, having a cryopreserved sample appears to at least double the chances of paternity.
Quality of life	k=1 cohort study of those who achieved paternity vs those who did not	⊕⊕⊖⊖ observational study	Achieved paternity vs did not: General QoL: 86.3 ± 16.4 vs 78.6 ± 19.6, p=0.018 Emotional functioning: 91.0 ± 15.1 vs 78.0 ± 22.0, p=0.001 EORTC QLQ-C30 and T26 questionnaires, scales 0 to 100, where high score represents higher level of functioning	Quality of life was higher in those who achieved paternity than those who did not.

^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.

EEJ = electro-ejaculation for aspermic patients; RR = relative risk; TESE = testicular sperm extraction for azoospermic patients; QoL = quality of life

On the basis of the benefits and harms reported in the evidence base (summarised above), the assessment suggested that relative to no cryopreservation, cryopreservation of sperm has non-inferior safety and superior effectiveness.

Clinical Claim

The clinical claim is that fertility preservation allows the potential for patients to have a biological family in the future with substantial improvements in their satisfaction and quality of life.

The addition of MBS items related to the processing and cryopreservation of male gonadal tissue and gametes will allow equity of access to fertility preservation technologies.

The claim is also that it will assist consistency in oncofertility referral pathways, so that patients have the opportunity to consult with a reproductive specialist, the opportunity to undertake fertility preservation, as well as receive oncofertility follow-up in the survivorship period.

12. Economic evaluation

The application presented:

- Limited cost analysis of the cryopreservation of testicular tissue, and
- Cost-effectiveness analysis of the cryopreservation of sperm.

Given there is little clinical evidence and no conclusion regarding the effectiveness of gonadal tissue cryopreservation, a full economic evaluation is not able to be undertaken for this proposed listing. A costs-only analysis estimates the total costs per patient associated with gonadal tissue cryopreservation to be, on average, \$2,570 per patient.

On the basis of the clinical conclusion; that sperm cryopreservation in males, has increased effectiveness for parenting outcomes; a cost-effectiveness evaluation has been performed.

Table 6 Summary of the economic evaluations (of sperm cryopreservation)

Perspective	Australian healthcare system
Comparator	No cryopreservation
Type of economic evaluation	Cost-effectiveness, cost-consequences, partial cost-utility
Sources of evidence	Systematic review
Time horizon	10 years for an adult population and 25 years for adolescents
Outcomes	Cost per patient, cost per additional parenthood, cost per extra live birth, cost per parent-QALY gained
Methods used to generate results	Decision tree analysis
Cycle length	One year
Discount rate	5% for both costs and effectiveness
Software packages used	Microsoft Excel 2013

QALY = quality-adjusted life year

The overall costs and outcomes, and incremental costs and outcomes as calculated over a cohort of 100 males/couples for the intervention and comparator in the model, and using the base case assumptions are shown in

Table 7.

Table 7 ICERs: fertility preservation compared with no fertility preservation, cohort of 100 males*/couples (discounted analysis)

	Fertility preservation	No fertility preservation	Increment	ICER (\$/outcome)
Cost	\$467,363	\$134,207	\$333,156	
Clinical outcomes				
Achieving parenthood	5.04 couples	2.16 couples	2.88 couples	\$115,602 / additional male (or couple) achieving parenthood
Live births	7.90 births	3.71 births	4.20 births	\$79,399 / additional live birth
Parent-QALYs	18.15 QALYs	17.24 QALYs	0.91 QALYs	\$365,826 / additional parent-QALYs gained

* For males who are adult at diagnosis

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years

For males who are adolescent at diagnosis the (discounted) ICERs are calculated to be:

- \$431,858 per additional patient achieving parenthood
- \$296,616 per additional live birth, and
- \$1,173,978 / additional QALYs gained.

These key sensitivity analyses for males who are adult at diagnosis are presented in terms of the outcome of cost per live birth. The modelled results were most sensitive to the usage rate (banked sperm in intervention arm or TESE in comparator arm). The results were also sensitive to the success rate of ART using fresh or banked sperm and storage costs of cryopreserved sperm.

13. Financial/budgetary impacts

To estimate the number of proposed services that would be performed in Australia, a mix of epidemiological and market approaches is used.

The financial implications to the MBS resulting from the proposed listing of processing and cryopreservation of semen and testicular tissue are summarised in Table 8.

Table 8 Total costs to the MBS associated with semen and tissue processing and cryopreservation

-	Year 1	Year 2	Year 3	Year 4	Year 5
Semen cryopreservation	-	-	-	-	-
Number of services	4,243	4,311	4,380	4,450	4,521
Sub-total cost	\$1,781,366	\$1,809,868	\$1,838,826	\$1,868,247	\$1,898,139
Tissue cryopreservation	-	-	-	-	-
Number of services	34	35	35	36	36
Sub-total cost	\$17,217	\$17,492	\$17,772	\$18,057	\$18,346
Total services	4,277	4,345	4,415	4,486	4,557
Total cost to MBS	\$1,798,583	\$1,827,361	\$1,856,598	\$1,886,304	\$1,916,485

MBS = Medicare Benefits Schedule

The proposed item for processing and cryopreservation of testicular tissue for fertility preservation is to be used with MBS items 37605 and 37606 for surgical collection of tissue. Fertility preservation for the proposed population is currently in (non-MBS funded) practice in Australia, but items 37605 and 37606 can (and are) already claimed in association with the service. Little growth is anticipated in services for processing and cryopreservation of testicular tissue if it were to be listed on the MBS, and therefore little impact on the usage of MBS items 37605 and 37606 is expected.

Cryopreserved samples of semen or tissue incur an annual storage cost of \$370 – \$500 which

is not covered by MBS or private healthcare funds, and is borne by the patients or their guardians.

14. Key issues from ESC for MSAC

This application relates to the processing, analysis and cryopreservation (freezing) of testicular tissue and sperm to preserve fertility in men undergoing gonadotoxic treatment.

ESC noted that collection of sperm for this purpose for men who cannot produce a sperm sample is currently covered on the MBS under item numbers 37605 and 37606 for testicular sperm extraction (TESE) and item numbers 13290 and 13292 for electro-ejaculation (EEJ). ESC noted that there are two populations addressed in the application:

1. Processing and cryopreservation of semen or testicular tissue in post-pubertal males (adolescents and adults) undergoing gonadotoxic treatment.
2. Testicular tissue biopsy, processing and cryopreservation in pre-pubertal children undergoing gonadotoxic treatment in the hope that future technology may allow the re-implantation of the tissue or spermatogonial stem cells.

ESC noted that there is currently no evidence in pre-pubertal boys that testicular tissue extraction and later re-implantation of testicular tissue or spermatogonial stem cells improves fertility. As this procedure is experimental, ESC agreed with the sponsor's proposal to review the technology in this population in three years if evidence becomes available. A future re-submission from the applicant would be required to commence this process.

ESC noted that, if integral to the delivery of the service, the definition of semen cycles and limits on the number of semen collection cycles should be included in the item descriptor rather than in the explanatory notes. ESC also questioned whether there should be an age minimum included in the descriptor for consistency with the evidence available.

ESC advised that storage costs should be separate from collection and processing as the cost of storage should not be covered by the MBS.

ESC questioned whether a period of six months storage is intended to be included in the proposed service and the benefit of the inclusion of six months of storage in the proposed service, as suggested in the economic model, given that patients undergoing gonadotoxic treatment are unlikely to be in a position to use the samples within six months.

ESC acknowledged an initial period of storage would give patients time to make decisions on fertility.

ESC questioned whether storage meets the *Health Insurance Act 1973* definition of a health 'professional service' and noted that inclusion of the cost of storage for this service would require a new government initiative (i.e. outside the MBS) and would set a precedent for similar items. ESC noted that with subsequent storage costs borne by the patient, the ongoing cost of storage may impose a substantial financial burden on patients, introducing equity concerns. ESC questioned whether there are any other options or funding models available for the storage costs for cryopreserved samples.

ESC requested that additional real-world data be provided on the duration of storage for patients of different ages and who would be likely to cover the cost of storage. ESC noted that the duration of storage information provided in the application is confounded because it is from patients who have already decided to pay for the service.

ESC noted a number of ethical issues associated with the proposed service including:

- the existence of inequitable barriers to fertility preservation due to cost;

- issues of male identity associated with fertility preservation;
- the need for adequate counselling (particularly for adolescents);
- the need for patients to be offered fertility preservation prior to treatment; and
- issues of storage of tissue after the death of a donor.

ESC noted that some of these issues may be addressed by the National Health and Medical Research Council's 'Ethical guidelines on the use of assisted reproductive technology in clinical practice and research', which was updated in 2017.

ESC noted that the comparator of no cryopreservation, including invasive procedures to extract sperm if they become azoospermic or aspermic and wish to conceive, is appropriate.

ESC noted there are no safety issues for the patient for cryopreservation of sperm prior to treatment. ESC noted that testicular tissue retrieval is invasive and requires anaesthesia which has associated risks, though no complications were reported in the studies presented (k = 5, n = 86). ESC noted that EEJ also requires anaesthesia, with its associated risks, with one complication reported (pneumonia due to pulmonary aspiration) in the studies presented (k = 2, n = 71). ESC concluded that cryopreservation prior to gonadotoxic treatment is likely to be safer than the absence of cryopreservation as it avoids invasive procedures. In males who don't undergo cryopreservation prior to treatment, cryopreserving EEJ or TESE samples will save repeat procedures for subsequent future assistive reproductive therapy (ART) cycles.

ESC noted that overall the quality of clinical evidence presented was low, and based on small observational studies. ESC noted that a meta-analysis of four studies was presented showing male cancer patients with cryopreserved sperm were more likely to father a biological child compared with those who did not cryopreserve. ESC noted that this evidence is confounded as men wishing to have biological children are more likely to undergo cryopreservation.

ESC noted that the clinical evidence for pregnancies and live births following ART resulting from cryopreservation of sperm prior to gonadotoxic treatment compared with fresh sperm following gonadotoxic treatment (collected by ejaculation or TESE) is based on observational studies in small series of patients (n < 100 for each).

ESC noted that this evidence suggests that the live birth rate is similar for these two populations. ESC noted that on the basis of the clinical evidence it is suggested that, relative to no cryopreservation, cryopreservation of sperm in post-pubertal males after completion of gonadotoxic treatment has superior safety and non-inferior effectiveness.

ESC considered the evidence presented for the live birth rate for men who cryopreserved sperm prior to gonadotoxic treatment compared with men who become azoospermic or aspermic due to treatment and underwent TESE. ESC noted that this evidence suggests that having a cryopreserved sperm sample prior to gonadotoxic treatment doubles the chances that the male will be able to have a biological child, compared to attempted TESE after treatment.

ESC noted that a cost-effectiveness evaluation was performed for sperm cryopreservation compared with no cryopreservation.

ESC noted that applicability issues were not addressed in the application and considered that this was inappropriate. ESC noted that the model was highly sensitive to many assumptions used in the modelling. ESC noted that it appeared that the outcomes used in the model were not consistent with outcomes presented in Section B of the application, specifically:

- the value used in the model for the proportion of patients who use the cryopreserved sperm is 8% (for males aged 12–76) whereas the data from Section B indicate that 10% of patients 18–60 years used their cryopreserved sperm;

- ESC questioned the upper value of 60% used in the sensitivity analysis as only around one third of men would become infertile as a result of gonadotoxic treatment; and
- an ART success rate of 77% for was used in the model (66% for patients undergoing TESE), compared with the success rate of around 50% presented in Section B of the application.

ESC noted other assumptions that were not justified were that:

- the proportion of patients in the comparator arm undergoing ART was assumed to be the same as the intervention arm; and
- QALYs appeared to accrue in the model for one parent only, however the model suggests that it has accounted for QALYs in both parents.

ESC noted that the model does not follow the structure presented in Figure 7 of the Assessment Report. ESC noted that the economic modelling uses clinical benefits and usage rates that are highly uncertain as they are based on outcomes from observational studies.

ESC noted the following main issues with the economic modelling presented:

- the model structure doesn't allow for cross-over of treatment;
- the costs for ART were a substantial proportion of the total cost for both the proposed service and the comparator. ESC noted that an average cost for ART was applied in each treatment arm, regardless of success, which may not represent the actual cost of moving to more expensive ART options where initial attempts are not successful;
- the increase in QALYs in the model was small and the model was driven largely by inclusion of storage costs, despite this cost being borne by patients. If storage costs are removed the ICER decreases from \$431,000 per QALY to around \$50,000 per QALY; and
- if patients choose not to continue storage after six months the overall health outcomes associated with the service would be vastly reduced. ESC noted that there is some evidence provided in the submission regarding storage lengths and drop outs, however it is questionable whether these rates are applicable to a situation where storage for the first six months is at no cost to the patient. ESC advised that storage costs should be separate from collection and processing as the cost of storage should not be covered by MBS.

ESC noted that the cost-effectiveness analysis for this type of treatment is difficult to interpret as it is difficult to put a value on becoming a parent. ESC suggested a cost per live birth as presented may be the appropriate primary cost-effectiveness analysis. ESC noted that some consideration of costs and outcomes from a societal perspective may have been informative for this application.

ESC noted that the eligible population in the financial estimates is based on current MBS statistics for patients with gamete/tissue collection and one or both of chemotherapy and radiotherapy within a financial year. ESC noted that this may not be a reasonable approach as it would underestimate utilisation of the service if listing increases the uptake of fertility preservation, which ESC considered would be likely.

ESC noted strong consumer advocacy for access to cryopreservation of semen for fertility preservation. However, it is important to consider the cost to consumers for the proposed service and the ethical issues raised in the application.

ESC noted that counselling is encouraged as part of the fertility preservation process and noted that this will be addressed as part of MSAC application 1438, not yet submitted to the Department. ESC noted that under NHMRC guidelines there is currently a requirement for clinics to provide access to counselling for certain circumstances.

ESC Key ISSUES	ESC ADVICE
Evidence	No evidence of effectiveness or safety for cryopreservation in prepubertal boys – The descriptor requires clarification of the minimum age.
Item descriptor	Storage costs are not covered by MBS or health funds. Application includes initial 6 months storage. If the application is successful with storage an included component, a new government initiative (i.e. outside the MBS) would be required as storage is not a health professional service as required by the <i>Health Insurance Act 1973</i> .
Proposed Fee	Fee includes 6 months of storage. Above point: policy request clear separation between collection/processing vs storage.
Item descriptor	Renaming of Item 2 to include ‘Semen collection’ and specifier of ‘maximum 2 cycles collection, if integral to the service
Future linked application	Counselling (psychosocial) encouraged as part of this process (future application to be proposed)

15. Other significant factors

Nil

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

The applicant had no comment.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)