Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1331 – Review of archival tissue for further diagnostic testing

Applicant: **The Royal College of Pathologists of Australasia**

Date of MSAC consideration: **69th MSAC Meeting, 6-7 April 2017**
68th MSAC Meeting, 24-25 November 2016

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

1. Purpose of application and links to other applications

An application requesting a new Medicare Benefits Schedule (MBS) listing of the retrieval and review of archival tissue by pathologists for further diagnostic testing was received by the Department of Health from the Royal College of Pathologists of Australasia (RCPA).

The proposed medical service is the review of archival tissue by a pathologist to select appropriate tissue samples, predominantly cancer tissues, for further testing or pathological review. Currently there are no formal arrangements for public or private reimbursement for the retrieval and review of archival tissue by a pathologist in Australia.

2. MSAC's advice to the Minister – April 2017 consideration

After considering additional information provided by the Department and the applicant, and the strength of the available evidence on comparative safety, effectiveness and cost-effectiveness, MSAC supported the listing of an MBS item for the retrieval and review of archival tissue by pathologists for further diagnostic testing.

MSAC supported MBS funding for review of archival tissue for further diagnostic testing with:

a) refinement of the proposed item descriptor wording to limit this testing to genetic tests from *Group P7 – Genetics* of the Schedule;
b) setting the MBS fee for the proposed item at $85 reflective of the professional service only not including administrative costs; and
c) limiting the proposed item to one retrieval of archival tissue per patient episode.

MSAC proposed the following descriptor:

Category 6 – PATHOLOGY SERVICES
MBS ##### The retrieval and review of archived tissue block(s), including specimen dissection, all tissue processing, staining, light microscopy, and professional opinion or opinions, by a pathologist to determine the appropriate sample(s) for further diagnostic testing. The diagnostic test(s) must be listed in *Group P7 – Genetics* of this Schedule. Limited to one retrieval per patient episode. Fee: $85.00 Benefit: 85% = $72.25; 75% = $63.75 Note: Retrieval of patient tissue blocks from pathology laboratory archives should only be performed for the purpose of conducting further essential genetic testing; the test(s) must be specified in the pathology request form and the test(s) must be performed within the same patient episode as the retrieval service. Tissue blocks previously prepared from cytology specimens, prior to archival storage, are acceptable but this item does not apply if services in *Group P6 – Cytology* are rendered in the same patient episode as the retrieval service, as specified in P.19.1 of the Medicare Benefits Schedule, under *Tests on Biopsy Material*. Not to be co-claimed with items 72858, 72859.

Summary of consideration and rationale for MSAC's advice – April 2017

MSAC noted that it had previously considered the listing of an MBS item for the retrieval and review of archival tissue by pathologists for further diagnostic testing at the November 2016 meeting. MSAC recalled that there was a case for public funding for this service, albeit for a narrower population, but that it had deferred its decision until further information on implementation and the proposed fee that was provided.

MSAC recalled that it had previously accepted that there were no safety issues with the service. In addition, MSAC recalled that although there were some difficulties in assessing the effectiveness and cost-effectiveness of the service, it was considered best practice and there was a case for funding the service (MSAC Public Summary Document (PSD) Application 1331, November 2016).

MSAC recalled that it had asked for the item to be restricted to retrieval of tissue for testing where urgency was vital for consequential treatment options (e.g. genetic testing to determine eligibility for PBS-subsidised cancer treatment). MSAC agreed that restricting use of the item to tests included in *Group P7 – Genetics* of the Pathology Services Table would limit the use of the item appropriately and ensure that genetic tests added to the MBS in the future are also eligible.

MSAC accepted that use of this item could not exclude use for research and clinical trial purposes. However, MSAC noted that limiting subsidies to items already listed on the MBS in *Group P7 – Genetics* would restrict use of the item to genetic tests that had already been accepted to be safe, effective and cost-effective during previous MSAC deliberations.

MSAC had previously queried whether including a time limit in the item descriptor was feasible. MSAC agreed with a proposal to include a rule in the item descriptor that the retrieval and review item and the listed *Group P7 – Genetics* item should be rendered in a single Patient Episode Initiation (PEI). MSAC noted that under the PEI rules testing must be conducted within 14 days for a retrieval claim to be valid. MSAC noted that this should reduce turnaround time without specifying a time limit in the item descriptor. In addition, MSAC noted that the RCPA had proposed that a measure of the time from receiving a request to retrieve and review archived tissue to the shipping of the slides to the testing laboratory could be incorporated into its quality assurance program. The RCPA suggested that reporting of this measure was also likely to improve turnaround times. MSAC suggested that the RCPA could conduct a random annual audit of this measure to monitor turnaround times.

MSAC had previously agreed that the item should also be able to be used to retrieve and review appropriate cytology specimens. MSAC agreed that including a note in the item that cytology specimens are acceptable as long as no *Group P6 – Cytology* services are rendered in the same PEI was a workable solution.

MSAC recalled that it had requested a more detailed justification of the $150 proposed fee for the service. MSAC noted advice from the RCPA that if a pathologist was not required to review large numbers of blocks, the minimum the cost for the service would be $90 (including a small amount [$5] for administration which cannot be funded under the MBS). MSAC also noted RCPA advice that it was prepared to accept a reduction in the proposed $150 fee. MSAC noted Departmental advice that current MBS fees for examination of biopsy material with one or more tissue blocks, including specimen dissection, tissue processing, staining, light microscopy and professional opinion was approximately $71 for complexity level 2 (MBS item 72813) and approximately $86 for complexity level 3 (MBS item 72816). MSAC considered that identification of blocks that are suitable for retesting at the time of collection is becoming more common, making it increasingly likely that pathologists will not need to review a large number of blocks. Given this additional information, MSAC suggested that a reduced fee of $85 would be reasonable.

MSAC reiterated that this item could only be used if separate laboratories were involved in retrieval and testing. MSAC suggested that the payment for this item should be made to the laboratory retrieving the sample. MSAC also reiterated that this item cannot be claimed in conjunction with MBS items 72858 or 72859 (second opinion on a patient specimen). MSAC noted that use of the item should be restricted to one retrieval of archival tissue per patient episode.

MSAC's advice to the Minister – November 2016 consideration

After considering the strength of the available evidence presented in relation to the comparative safety, clinical effectiveness and cost effectiveness, MSAC deferred the listing of an MBS item for the retrieval and review of archival tissue by pathologists for further diagnostic testing. MSAC advised that this service had a place for public funding, but with a narrower focus than that presented in the application before the Committee.

MSAC requested the following information before it could finalise its advice:

- Modification of the proposed MBS item descriptor to:
    - link this service only with MBS or PBS items representing consequential treatment options where urgency is vital;
    - exclude services where retrieval is undertaken simply to review morphology or immunostaining; these should be performed using second opinion item numbers 72858 and 72859;
    - allow the service with cytology specimens;
    - exclude its use for research or clinical trials; and
    - clarification or removal of the 7 day time limit.
- Further details from the Department on potential implementation options and the feasibility of each option, particularly if a time period is included in the descriptor, to define exactly when this period starts and ends and to outline the proposed framework to monitor compliance with this time period.
- A more detailed justification of the proposed $150 fee, including comparison with other fee setting and breakdown of the pathologist time (review) and business components (eg retrieval of blocks and preparation for review and transport).

- Ensure that the item should only apply when retrieval/review is performed in a different laboratory to the laboratory that performs the requested test as the cost of retrieving/reviewing is likely already included in the cost of the test.

The response would be provided back to the next appropriate MSAC meeting.

Summary of consideration and rationale for MSAC's advice – November 2016

MSAC noted that use of archival tissue for testing avoided the need for patients to be re-biopsied and that review of archival tissue prior to testing was accepted best practice. MSAC noted that the argument for MBS funding of the service was that payment would prioritise retrieval and review of archived tissue, leading to faster fulfilment of requests for such tissue and this may improve patient care. However, MSAC noted that no direct evidence was presented to allow it to determine if providing such a payment improved compliance, turnaround time or patient outcomes.

MSAC accepted that there were no safety issues with the service.

MSAC noted that a single Australian study, reporting the results of an audit of *KRAS* mutation testing conducted on 3,688 metastatic colorectal cancer cases from four major pathology service providers, found that only 38% of tests were received by the testing laboratory within seven days (Scott R et al 2014).

MSAC noted that review of archival tissue prior to testing was accepted best practice and as such evidence of the clinical utility of such a service was lacking. As a consequence, MSAC noted that a linked evidence approach was used in an attempt to estimate the effectiveness and cost-effectiveness of the service. This approach assumed that funding the service would increase the proportion of tests turned around within seven days from 38% (as per Scott R et al 2014) to 100% and that the proportion of non-diagnostic tests that result from poor tissue samples being tested would fall from 13.3% to 8.3% with review. This data was then linked with data on test diagnostic performance, re-biopsy rates, decisions about therapy and the incremental costs and benefits of therapy initiated after diagnostic testing.

It was assumed that the patients most likely to benefit from the service were cancer patients undergoing molecular diagnostic tests that are already listed on the MBS (such as items 73332, 73336, 73337, 73338, 73341 and 73342), used to determine eligibility for Pharmaceutical Benefits Schedule (PBS) -subsidised cancer treatments. For this reason, incremental costs and benefits of PBS-subsidised therapy were modelled using publicly available data from a 2010 PBAC submission on the use of cetuximab to treat patients with metastatic colorectal cancer.

Two of the comparators were dominated (more expensive with poorer outcomes) by MBS funding for the service. For retrieval without review by a pathologist this was because it was assumed to result in higher rates of futile testing due to poor tissue samples being sent to the reference laboratory, higher rates of re-biopsy and reduced diagnostic accuracy that may inappropriately assign patients to PBS-subsidised treatment. MSAC considered that retrieval without review was unlikely to occur in Australian laboratories because pathologist review is a requirement for laboratories to meet professional standards. For immediate biopsy without retrieval of archived tissue this was because the re-biopsy procedure increased costs and reduced quality of life.

Compared with unfunded retrieval and review (current practice), the funded service would incur an incremental cost of $615 and lead to a gain of 0.0077 QALYs, resulting in an ICER

of $79,363 per QALY. The main drivers of this model were the proportion of tests being retrieved and reviewed within seven days and the incremental costs and cost-effectiveness of PBS-subsidised treatment.

Compared with no testing (precluding the patient from accessing PBS-subsidised treatment), the funded service would result in an ICER of $67,247 per QALY. The main drivers of this model were the costs and cost-effectiveness of PBS-subsidised treatment, not the test itself.

As highlighted by ESC, there were inherent difficulties in applying a cost-effectiveness approach to this service and there were many uncertainties included in the assumptions made in the model. ESC highlighted that the approach was unlikely to reflect the full benefits of the service, but that retrieval of archived tissue for further testing was fundamentally desirable for the patient. While the cost to the MBS of the service was estimated to be approximately $1.0 million per year, this was also uncertain, particularly if the service could be used for tests other than molecular diagnostic tests.

Considering the evidence before it, MSAC expressed concerns about whether the purpose of an MBS item was to increase timely retrieval and review of archived tissue or whether it was to fund a service already being provided on an unfunded basis that has increased in volume due to availability of new treatments. MSAC noted that no direct evidence was presented to allow it to determine if providing such a payment improved compliance, turnaround time or patient outcomes. MSAC was uncertain if the listing of this service, particularly if a time limit was imposed for payment, would shift priorities within laboratories with subsequent adverse effects upon other pathology services.

MSAC expressed reservations about including a time limit in the item descriptor for retrieval and review of archival tissue. MSAC acknowledged that there could be instances where delays in testing to determine eligibility for MBS- or PBS-subsidised therapies may adversely impact upon patient outcomes. For example, delays in testing to determine eligibility for a PBS-subsidised cancer therapy could cause harm if the cancer then progresses to a point where there would no longer be any benefit to treatment. MSAC requested further information on which particular tests to determine eligibility for subsequent treatment required such urgent turnarounds and indicated that any MBS funding for such a service was likely to be restricted to testing that is known to be time critical.

MSAC was also concerned that including a time limit could have unintended consequences if the patient is charged for the service because the timeframe for reimbursement was not met.

MSAC requested a more detailed justification of the $150 proposed fee for the service, including breakdowns of pathologist time, the administrative or business costs of providing the service and comparisons with other fees.

MSAC noted that implementing any MBS item for retrieval and review of archival tissue, particularly if the descriptor included a time limit, would not be straight forward. MSAC suggested that advice from the Department and/or the RCPA be sought on the following issues:

- Whether there are other models of funding that would better address this issue?
- How will the timeframe for reimbursement be monitored and enforced? Could this instead be managed through a Quality Assurance Program as a timeframe from request to tissue receipt?
- When does the timeframe for reimbursement begin and end?
- How will payments be distributed if one or two separate laboratories or pathology providers are involved in the service?

- Would the item number be claimed for cases where blocks suitable for future molecular testing were identified in the original histopathological report?

Finally, MSAC foreshadowed that:

- Use of this item would be limited to genetic testing but would be payable for retrieval and review of archived cytology specimens as well as archived tissue samples.
- Any future MBS item for the review and retrieval of archived tissue could not be claimed by the same laboratory/pathology provider in conjunction with MBS items 72858 or 72859 (second opinion on a patient specimen).
- Use of this item would exclude use for research and clinical trial purposes.

3. Background

MSAC has not previously considered the retrieval and review of archival tissue by pathologists for further diagnostic testing.

4. Prerequisites to implementation of any funding advice

Medicare benefits are only payable for pathology services if:

- approved services are performed in a laboratory within an appropriate Accredited Pathology Laboratory (APL) category;
- the service is rendered by or on behalf of an Approved Pathology Practitioner (APP); and
- the proprietor of the laboratory is an Approved Pathology Authority (APA)

5. Proposal for public funding

The proposed MBS item descriptor is summarised in Table 1.

Table 1 Proposed MBS item descriptor

Category 6 – PATHOLOGY SERVICES
MBS ##### The retrieval and review of archival tissue(s) by a pathologist to determine the appropriate sample(s) for further diagnostic testing within 7 days of receipt of the request. Limited to one retrieval per request. Fee: $150.00 Benefit: 85% = $127.50; 75% = $112.00

Abbreviations: MBS: Medicare Benefits Schedule

Due to the emphasis on the timeliness of the retrieval and review of archive tissue to inform clinical decision-making, a time limit was proposed from the date of request. There should be only one retrieval per patient sample, but multiple retrievals per patient can be requested with no maximum number specified (this would be an unusual clinical situation).

Although there are direct and indirect practice costs associated with tissue retrieval, most of the cost is related to the professional activities of the pathologist at the source laboratory in the pre-service and intra-service phases. The RCPA suggested these activities take in the range of 10-30 minutes and include the assessment of the samples representing a cost of approximately $50 to $120. The actual cutting of blocks and preparation of the slides, which, although not always performed by the pathologist, is always performed by a skilled professional medical or scientific practitioner (usually a pathology technician) under the supervision of a pathologist, is part of the professional service and the cost has been estimated by the RCPA to be in the order of $10 to $40. Additionally, there are the administration costs associated with the retrieval from the archive (on-site or off-site)

estimated by the RCPA to be between $25 and $45; this cannot be reimbursed by Medicare. An indicative fee for this service charged by one public sector provider is $150.

6. Summary of Public Consultation Feedback/Consumer Issues

No feedback was received on the Consultation Protocol.

7. Proposed intervention's place in clinical management

Advances in genetics and pharmacogenomics have resulted in a burgeoning array of targeted therapies based on specific 'typing' of the condition by a pathologist resulting in better management. For instance, treatment is often matched to a particular mutation in that patient's cancer. This may mean re-testing tissue that was collected at a previous biopsy/operation or tissue collected from affected relatives. Occasionally, the original tissue is collected at a place (e.g. regional/remote or non-specialist centres) or at a time when these tests cannot be performed or before a particular therapy is necessary or available. Pathologists are being increasingly asked to retrieve and review archival tissue specimens (blocks/slides) from patients with previous cancer diagnoses in order to select appropriate material to send for specialised biomarker testing to facilitate individualised therapy. This retrieval and review (the proposed medical service) is currently unfunded.

Figure 1 outlines the phases of process for diagnostic testing of tumour biopsy and the place of retrieval and review of archival tissue in that process. The overall turnaround time from test request to test result largely depends on the time for the retrieval and review of the archival tissue sample and the time from when the sample is received by the testing facility to the time the results are reported to the specialist. The optimal treatment management of the patient will depend on the outcome and timeliness of the test result.

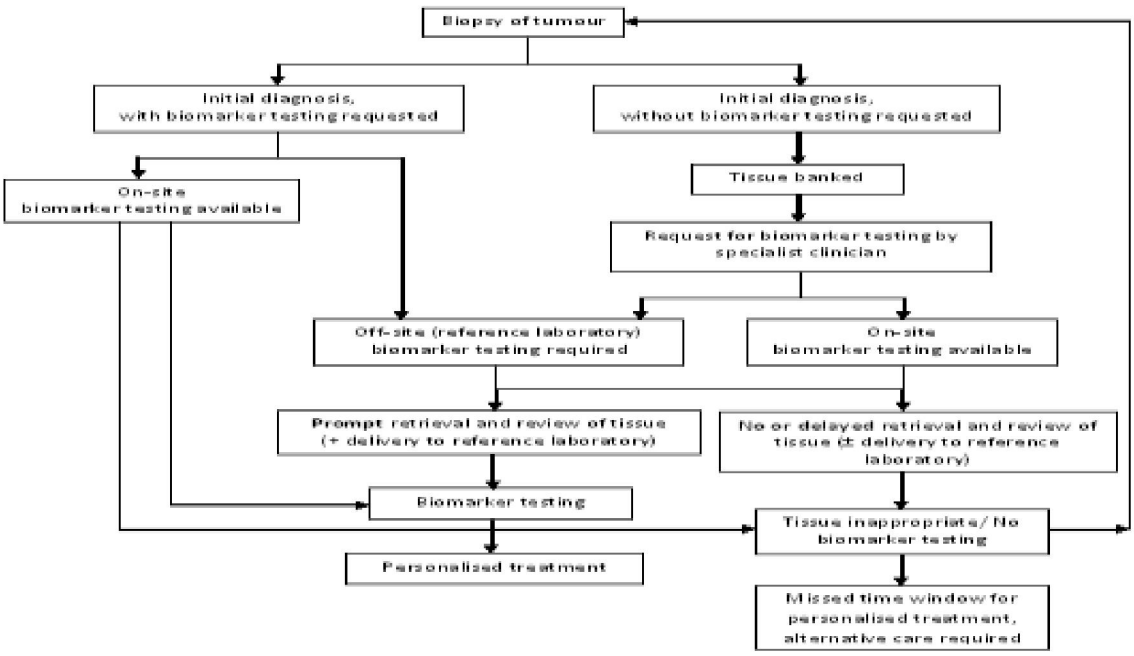

Figure 1The investigational algorithm and the place of the retrieval and review of tissue samples

The main departures from the Protocol relate to the patient population and the comparators considered in the assessment. Deviations from the Protocol are summarised and justified in Table 2.

Table 2 Patient Intervention Comparator Outocmes (PICO) items which deviate from the Decision Analytic Protocol (DAP)

PICO element	Patients	Comparator
Items as specified in the DAP	Patients who have conditions which may benefit from further testing of previously biopsied archived tissue, e.g., patients with cancer and other patients with diseases of genetic origin.	Retrieval of archived tissue without review by a pathologist No retrieval (and no diagnostic testing), with or without the ability to acquire a new tissue sample
Approach taken in the assessment	The systematic literature review focuses on patients who have cancer conditions which may benefit from current MBS funded tests on previously biopsied archived tissue for assessing eligibility for PBS funded co-dependent therapies. The economic analysis focuses on patients with mCRC which may benefit from KRAS mutation analysis of previously biopsied archived tissue.	Retrieval without review by a pathologist No retrieval and patient referred directly for biopsy No retrieval, no test, and patient remains ineligible for PBS drug (receives Biopharmaceutics Classification System); this also reflects a scenario whereby the cost of the retrieve/review process is incorporated in to the original decision to fund the co-dependent technologies. Retrieval and review by a pathologist without reimbursement (current practice)
Justification for change	This is considered appropriate on the basis the service will primarily be used within this context and this is where the most evidence is available to inform meaningful clinical and economic evaluations.	The first three comparators in the assessment are essentially the same as those outlined in the DAP, the only change being the second comparison in the DAP ("No retrieval of archival tissue (and no diagnostic testing), with or without the ability to acquire a new tissue sample") has been broken down for simplification into two comparators (No retrieval and patient referred directly for biopsy; No retrieval, no test, and patient remains ineligible for PBS drug).

8. Comparator

The proposed comparators for MBS funded retrieval and review of archival tissue are:

- retrieval without review by a pathologist;
- no retrieval and patient referred directly for biopsy;
- no retrieval, no test, and patient remains ineligible for PBS drug (receives best supportive care [BSC]); and
- retrieval and review by a pathologist without reimbursement (current practice).

The first three comparators are essentially the same as those outlined in the Protocol. The second comparison in the Protocol ("No retrieval of archival tissue [and no diagnostic testing], with or without the ability to acquire a new tissue sample") has been broken down for simplification in to two comparators (No retrieval and patient referred directly for biopsy; No retrieval, no test, and patient remains ineligible for PBS drug). The final comparator (unfunded retrieval and review) was included in the assessment following advice provided by PASC.

9. Comparative safety

MSAC accepted that there were no safety issues with the service.

10. Comparative effectiveness

The clinical claim is that incentivising pathologists to prioritise the review and referral of archival material for specialised testing upon request will lead to faster compliance with requests which may result in improved patient care.

In the absence of direct data, a linked evidence approach was presented in the context of diagnostic testing using archival tissue samples in relation to test failure and re-biopsy rates, test turnaround times, diagnostic performance, survival outcomes and costs and benefits according to treatment received and tumour genotype, and/or the incremental cost and incremental benefit of receiving targeted therapy compared to standard therapy according to tumour genotype.

The evidence base is disparate in terms of the tests conducted, the tissues upon which they have been performed, the testing methodologies employed and equipment available, the context in which the testing was conducted (pathology service or research), the setting and location of the testing and the contemporaneousness of the data collection. As such the data is not amenable to any meaningful pooling.

Test turnaround times
Collectively, the available data regarding overall test turnaround times indicate the consensus for maximally accepted turnaround time (3 weeks; 15 working days) is not being met in many cases. The data also suggest the time taken from ordering of test to receipt of sample at test facility (which includes the retrieval of tissue) contributes significantly to the overall test turnaround time and is frequently longer than the proposed reimbursement target time of 7 days (or 5 working days). Data from the Australian setting (Scott et al, 2014) in relation to KRAS mutation testing in clinical practice found an overall test turnaround time of 3 weeks or longer was observed in more than 35% of cases and this was mostly attributable to a delay in receipt of the sample by the testing laboratory (2 weeks or longer in approximately 30% of cases).

Test failure rates
The proportion of test failures due to "No test" – where tissue was unavailable for testing due to the sample not being retrievable from the archive, or the tissue was retrievable but, upon review, was considered unsuitable for testing due to insufficient tissue quality or quantity – ranged from 0.1% to 15.0%. The proportion of test failures due to "Test without result" – where, on review, an archival tissue sample was deemed suitable for testing, but, on subsequent analysis, the sample has failed to yield an interpretable result – ranged from 0.3% to 16%, with most studies recording between 0.3% and 3.0%. Taken together, this data confirms that prior review by a pathologist can identify a proportion of archival tissues as being sub-optimal for the requested diagnostic test. However, a proportion of archival tissues which are deemed as suitable for testing will also fail to yield results despite the prior review.

Re-biopsy
Based on the sparse available data, not all failed tests result in re-biopsy and not all re-biopsies necessarily provide sufficient material for testing.

11. Economic evaluation

The modelled economic evaluation, based on KRAS testing in mCRC patients, is a cost-utility analysis which follows a linked evidence approach structured to capture the impact of:

- improved retrieval and review processing times versus current practice;
- improved test failure rates relative to no review;
- improved diagnostic accuracy relative to no review;
- the costs, time delays and outcomes of any biopsies required; and
- the costs and outcomes of downstream treatment allocation decisions.

A summary of the key characteristics of the modelled economic evaluation is given in Table 3.

Table 3 Summary of the economic evaluation

Perspective	The model takes the perspective of the Australian health care system. Only direct health care costs and quality of life of the patient are included in the analysis.
Comparator	The economic model uses four potential comparators Unfunded retrieve and review Retrieval without review No retrieval and patient referred to biopsy No retrieval and patient remains ineligible for PBS drug (receives BSC)
Type of economic evaluation	Cost-utility analysis
Sources of evidence	The output of the retrieve and review process is determined by the review of evidence presented in Section B. These outputs include test failure rates and test turnaround times. The implications of test inaccuracies are determined from a review of PBAC PSDs for the co-dependent technologies of KRAS testing with cetuximab (see Section C.4)
Time horizon	The time horizon of the model extends until all patients have received a test result (less than one year). Downstream costs and consequences of treatments indicated (or otherwise) are included in the economic model are entered based on results previously determined by the PBAC.
Outcomes	Incremental costs Incremental QALYs Time to test result Proportion of test results which are too late (patient already progressed) Number of biopsies Accuracy outcomes (true positive, true negative, false positive, false negative)
Methods used to generate results	The model is calculated using a decision tree (cohort expected value analysis)
Discount rate	Not applicable. Test results are determined within one year. Downstream costs and consequences of treatments indicated (or otherwise) included in the economic model are entered as net present values (based on results previously determined by the PBAC, which uses a 5% per annum discount rate)
Software packages used	TreeAge Pro

The overall costs and outcomes, and incremental costs and outcomes as calculated for the testing strategy and comparative testing strategy in the model, and using the base case assumptions, are shown in Table 4.

Table 4 Incremental cost-effectiveness of retrieve and review relative to each of the possible comparators using base case assumptions

Setting	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
Intervention					
Funded retrieve and review	$6,236.19	-	0.0927	-	
Comparators					-
Unfunded Retrieve / Review	$5,621.38	$614.81	0.0850	0.0077	$79,363
Retrieval without review	$6,602.95	-$366.76	0.0922	0.0005	DOMINANT
Biopsy	$7,480.84	-$1,244.65	0.0889	0.0038	DOMINANT
No test	$0.00	$6,236.19	0.0000	0.0927	$67,247

Funded retrieval and review dominates retrieval without review and re-biopsy, due to higher costs from additional tests, biopsies and inappropriate treatment allocation based on an unsuitable tissue sample.

Compared to unfunded retrieval and review, funded retrieval and review results in an ICER of $79,363, with an incremental cost of $615 and incremental QALY gains of 0.0077. Compared to no test, funded retrieval and review results in an ICER of $67,247, with an incremental cost of $6,236 and incremental QALY of 0.0927.

Sensitivity analyses
The main drivers of the cost-effectiveness of funded retrieval and review compared to unfunded retrieval were the change in the proportion of tests retrieved and reviewed within a week and the incremental costs and cost-effectiveness of the treatment being initiated. Funded retrieval and review remained dominant compared to either no review or to re-biopsy across a range of scenarios tested. This is due to higher costs associated with receiving misallocated treatment, and higher costs associated with biopsy, respectively.

The main drivers of the cost-effectiveness of funded retrieval and review versus no testing were the costs and cost-effectiveness of treatment itself. This suggests MSAC could consider the extent to which health technology assessment is the appropriate mechanism with which to determine whether this service should be included on the MBS. Assuming this retrieval and review process is integral to the operation of the test then it would be better assessed as a cost component when deciding to fund the test itself.

12. Financial/budgetary impacts

The financial implications to the MBS resulting from the proposed listing are summarised in **Table 5**.

For the current MBS funded pharmacogenetic tests which may be assisted by the proposed service (MBS items 73332, 73336, 73337, 73338, 73341 and 73342), a total of 8,036 episodes of the retrieval and review of archival tissue are estimated to be performed each year. The associated total cost to the MBS of the proposed retrieval and review service is estimated to be approximately $1.0 million. It should be noted, however, that the financial implications of the proposed service are subject to uncertainty because the range of tests to which the service could be applied may expand in the future and the extent of this expansion is difficult to foresee. Furthermore, there may be tests currently listed on the MBS other than the pharmacogenetic tests examined in this assessment to which this service may apply. The financial implications of any future tests which could potentially utilise the proposed service would need to be added to the financial implications predicted here.

Potential cost savings or additional costs resulting from funded retrieval and review are not estimated due to inherent uncertainties associated with the proposed service's impact on downstream treatment practice and outcomes.

Table 5 Total costs to the MBS associated with the proposed retrieve and review service

	2017-18	2018-19	2019-20	2020-21	2021-22
Number of services	7,374	7,374	7,374	7,374	7,374
Total cost to the MBS					
- Services at 85% benefit (at $127.50)	$835,815	$835,815	$835,815	$835,815	$835,815
- Services at 75% benefit (at $112.50)	$166,577	$166,577	$166,577	$166,577	$166,577
Total MBS	$1,002,392	$1,002,392	$1,002,392	$1,002,392	$1,002,392

13. Key issues from ESC for MSAC

ESC noted that retrieving and reviewing archival tissue is already accepted as part of current pathology practice; however, there is currently no formal arrangement for public or private reimbursement for this service by a pathologist in Australia

ESC agreed that this service is most likely to benefit patients with cancers treated with co-dependent therapies with any potential cost-effectiveness intrinsically linked to the cost-effectiveness of the co-dependent treatment. However, the data presented were limited and disparate, primarily modelled on metastatic colorectal cancer (mCRC). ESC was uncertain as to applicability of the mCRC model to other cancers and non-cancer clinical scenarios. No data were presented for the other (non-cancer) clinical scenarios and ESC considered there could be potential leakage and associated costs. ESC considered that applying a conventional cost-effectiveness approach to this type of service was inherently difficult and unlikely to reflect the true benefit of tissue retrieval for patients across multiple different indications and stages of treatment, but that retrieval of archival tissue for further testing was fundamentally desirable for the patient. ESC agreed that MSAC might wish to consider if this service should be restricted to reimbursed co-dependent therapies only, although the Applicant disagreed with this proposal in the pre-ESC response. The ESC noted that retrieval of archival tissue would potentially be for molecular pathology (sequencing), *in situ* hybridisation or immunohistochemistry (IHC).

ESC noted there were several uncertainties included in the Assessment report assumptions and results. For example it was assumed that if the retrieval and review was delayed then treatment is not possible, rather than the treatment being just delayed. There was also an assumption of 100% test accuracy. ESC also noted several typographical errors in the report.

ESC noted that the projected usage figures assume an inpatient and outpatient split which may be conservative. Also the projected figures do not account for the increasing likelihood of future reflex co-dependent testing at the time of diagnosis.

ESC queried whether the requested fee was reasonable, given that the reimbursed fee for a similar service in the United States is significantly lower. ESC noted that in Australia some laboratories absorb the costs of the retrieve and review service; however, a number of laboratories are charging patients (up to $175) as indicated in the Final Protocol.

Implementation issues
ESC questioned whether funding this service would enable testing within 7 days, noting that this timeframe could be difficult to monitor and enforce. ESC considered that the period to which the 7 days refers should be clearly stated to avoid any potential confusion, for example, 7 days from the date the request was written or 7 days from the date the pathologist received the request.

ESC agreed with the Department's concern that interpretation of the term 'request' could lead to leakage of the item with multiple claims for tissue retrieval per test and would require an explanatory note to limit the service to per test requested. ESC was also concerned that, if this service were to be MBS-subsidised, there could be inappropriate claiming of this item with non-MBS funded items and there could be potential for co-claiming with the "Second Opinion for Morphological/Interpretive Pathology" item recently supported by MSAC (Application 1332, MBS item 72858).

ESC also discussed potential funding options if one or two laboratories were involved in this service. ESC considered it was inappropriate for the laboratory to be able to co-claim this service if it is also conducting and claiming for the requested test fee. However, if two

separate laboratories are involved in the service, ESC considered that the source laboratory should be able to claim this service for retrieval of the archived tissue and the reference laboratory that reviews the tissue should only be able to claim the requested test fee.

Potential Options for MSAC consideration
ESC highlighted some potential funding considerations:

- no funding for the service;
- limit funding for the service to assessing eligibility for PBS-subsidised targeted therapies;
- full funding for the service with no restrictions (i.e. available for cancer, non-cancer, MBS or non-MBS downstream indications);
- limit funding to the retrieval (source) laboratory only but not if co-claiming the test – i.e. only the reference lab can claim the requested test fee; or
- allow the second opinion item claim (MBS item number 72858, $180) by retrieval (source) lab for this item only when co-claimed with the requested test for the funded co-dependent test by the reference lab; and
- whether this should be limited to archival tissue blocks or also to allow slides.

ESC considered that of these options, it would be appropriate for the downstream test to be an MBS item and that funding for retrieval should be limited to those services performed in a laboratory where the benefit from the MBS test item would be claimed by a separate reference laboratory. There should also be restrictions on laboratories attempting to claim this benefit solely by moving samples between sites within the same organisation.

ESC noted that stored slides were rarely suitable for IHC for longer than a few months and that the burden on pathologists was associated with retrieval of tissue blocks, requiring inspection of the block, differentiation of tissue/cell types present against the criteria necessary for the test requested, selection of target area for sectioning and so on. Cytology specimens were not considered relevant for this service.

14. Other significant factors

Nil

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

The new item should be restricted to diagnostic (non-research) purposes only, however should not be restricted to being linked to particular PBS and MBS items or particular "treatment options where urgency is vital" as this will limit access for small but important and evolving patient and treatment groups. Similarly, limiting the item to "genetic" testing is too proscriptive and immunohistochemistry or morphology per se should not be excluded as these can be important justifiable reasons for pathologist-led retrieval. Tissue retrieval is not covered by the second opinion item number. The specified time period (7 days) may be omitted from the item, however prompt retrieval should be supported in some other way such as explanatory notes and could be audited via quality assurance survey. An alternative fee could be considered but it must be appropriate to fund the pathologist time to review the tissue. Tissue retrieval is an intensive professional medical activity. Where "one or two separate laboratories or pathology providers are involved in the service" the payment should be made to the laboratory retrieving the sample. Please note as a factual error that although "MSAC considered that retrieval without review was unlikely to occur in Australian laboratories because pathologist review is a requirement for laboratories to meet professional standards", there is no such requirement in Australian laboratory standards.

16. Further information on MSAC

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