MSAC Application 1331

Final Protocol to guide the assessment of the retrieval and review of archival tissue by pathologists for further diagnostic testing

October 2015

FINAL

Table of Contents

FINAL

MSAC and PASC

The Medical Services Advisory Committee (MSAC) is an independent expert committee appointed by the Australian Government Health Minister to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health on the evidence relating to the safety, effectiveness, and cost-effectiveness of new and existing medical technologies and procedures and under what circumstances public funding should be supported.

The Protocol Advisory Sub-Committee (PASC) is a standing sub-committee of MSAC. Its primary objective is the determination of protocols to guide clinical and economic assessments of medical interventions proposed for public funding.

Purpose of this document

This document is intended to provide a draft decision analytic protocol (DAP) that will be used to guide the assessment of the retrieval and review of archival tissue by a pathologist to determine the appropriate tissue samples for further diagnostic testing. The draft protocol will be finalised after inviting relevant stakeholders to provide input. The final protocol will provide the basis for the assessment of the intervention.

The protocol guiding the assessment of the health intervention has been developed using the widely accepted "PICO" approach. The PICO approach involves a clear articulation of the following aspects of the research question that the assessment is intended to answer:

Patients – specification of the characteristics of the patients in whom the intervention is to be considered for use;
Intervention – specification of the proposed intervention;
Comparator – specification of the therapy most likely to be replaced by the proposed intervention; and
Outcomes – specification of the health outcomes and the healthcare resources likely to be affected by the introduction of the proposed intervention.

Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing for the retrieval and review of archival tissue by a pathologist to determine the appropriate tissue samples for further diagnostic testing was received from The Royal College of Pathologists of Australasia by the Department of Health in April 2015. The proposal relates predominantly to patients with cancer and is a new pathology investigational service, not currently listed on the MBS,

to retrieve archival tissue and identify appropriate samples for genetic and/or molecular testing (biomarker testing) for diagnostic, prognostic or therapeutic assessment services.

The Assessment Group at Griffith University, as part of its contract with the Department of Health, drafted this DAP to guide in the independent assessment of the proposed investigation in order to inform MSAC's decision-making regarding public funding of the intervention.

Background

Anatomical pathology tissue is any tissue that is biopsied or cut from a patient and excludes blood tissues. By law labs must retain anatomical pathology samples for 10 years, in case review or further diagnostic testing is required. Pathologists are increasingly retrieving and reviewing banked tissue to support individualised therapy based on information provided by new technologies. As medical knowledge continues to evolve, samples have a prospective value in the provision of patient care.[1]

An advantage of reviewing stored archival tissue is that, depending on the particular clinical situation, the patient may not need to undergo an invasive procedure to supply a new tissue sample. There are risks to the patient associated with providing an additional biopsy sample, especially in advanced disease, and the use of archival tissue, where possible, decreases the risk of adverse events and reduces associated hospital costs.

Current arrangements for public reimbursement

Currently there are no formal arrangements for public or private reimbursement for the retrieval and review of archival tissue by a pathologist in Australia. Although some laboratories do not charge for the service, choosing instead to absorb the costs, many and an increasing number of laboratories are charging patients (up to $175). Further there is anecdotal and systematic data to show lack of funding results in delays in tissue retrieval, which in-turn delays appropriate treatment and may result in sub-optimal patient care. This may be leading to considerable inequity between patients who often have secondary or advanced cancers.

Usually the requests to retrieve and review archival tissue are urgent, as patients are being assessed for suitability for new targeted drugs. Furthermore, review of archival tissue also has a role in identifying patients who may be eligible for clinical trials of new therapies. Although not performed routinely, the retrieval and review of archival tissue can take considerable time. There are no official statistics; however, it is estimated that the retrieval and review of archival tissue occurred approximately 1,325 times in 2014 (see Table 3).

As the retrieval of tissues is primarily to assess a cancer patient's suitability for new, targeted drugs which are listed on the Pharmaceutical Benefits Scheme (PBS), it has been suggested that the item could be specified to be co-dependent with pharmacogenomics tests (Pathology Services Table, Group P7 - Genetics). This may not be appropriate as there is a variety of other clinical scenarios that warrant tissue retrieval and which are vital to patient care.

MSAC has previously acknowledged the need for archival tissue retrieval and review and the costs involved in Public Summary Document #41 - Epidermal growth factor receptor (EGFR) gene testing and access to PBS listed gefitinib, suggesting that "overall costs for sample collection, retrieval and handling also need to be considered".[2]

Regulatory status

Pathology laboratories are required by law to retain anatomical pathology specimens (in the form of tissue blocks or slides) for a minimum of 10 years. This is regulated by National Pathology Accreditation Advisory Council (NPAAC) guidelines under the National Association of Testing Authorities (NATA) and State and Territory legislation. There are standards requiring the correct assessment and processing of tissue to ensure preservation for future diagnostic use, to be either performed, or supervised by, a pathologist. It should be noted that retention of tissue is a legal requirement the banking and preparation procedures do not qualify for payment of Medicare benefits (Section P1.3 of the Pathology Services Table in the MBS).

When requested, archival tissue is retrieved for further diagnostic testing including biomarkers and more latterly using *in vitro* diagnostic medical devices (IVDs). IVDs consist of the tests and related instrumentation used to carry out testing on human samples where the results are intended to assist in clinical diagnosis or in making decisions concerning clinical management, usually for the detection of a mutation as a prerequisite for access to PBS-subsidised medication. These tests may be used for identifying selective therapy and management options, for example in personalized medicine, and for disease staging.

The Therapeutic Goods Administration's regulatory framework for IVDs requires pathology laboratories to have received accreditation from NATA/RCPA. To gain NATA/RCPA accreditation a laboratory must satisfy standards set by the NPAAC.

The application for a MBS fee related to the retrieval, review and selection of archival tissue is substantially associated with the pathologist's time and expertise and the provision of a professional service. Under the Health Insurance Act 1973 (and also defined in Section P1.1 of the Pathology Services Table in the MBS), a professional service is defined as follows:

(d) a pathology service that is rendered by, or on behalf of, an approved pathology practitioner pursuant to a request made in accordance with subsection 16A(4) by:

(i) a treating practitioner; or

(ii) another approved pathology practitioner who received a request for the service made by the treating practitioner; or

(e) a pathology service (other than a service referred to in paragraph (d)) that is a clinically relevant service rendered by, or on behalf of, an approved pathology practitioner other than a medical practitioner.

According to the above definition, the retrieval and review of archival tissue for diagnostic purposes is a professional service requested by the treating practitioner and therefore should be eligible for MBS funding, should the service also be assessed as safe, effective and cost-effective. The service could be provided by an approved pathologist or under the supervision of an approved pathologist.

Intervention

Description

Advances in genetics and pharmacogenomics have resulted in a burgeoning array of targeted therapies based on specific 'typing' of the condition by a pathologist. For instance, treatment is often matched to a particular mutation in that patient's cancer in what is known as personalised medicine, resulting in better patient management. This may mean it is necessary to retest tissue that was collected at a previous biopsy or surgery to ascertain whether a particular therapy will be effective.

The proposed investigational service is the retrieval and review of archival tissue by a pathologist to select appropriate tissue samples for further testing or pathological review. This process may occur following progression of disease; however, it can also occur at the time of initial diagnosis.

As mentioned, pathology laboratories are required by law to retain anatomical pathology specimens for a minimum of 10 years. The numbers are such, that this archiving is often off-site. When further tests are requested following the progression of disease, pathologists are required to retrieve and review archival tissue and select appropriate samples so that the required tests can be performed either on-site or off-site at a reference laboratory (a large laboratory that is able to perform the specialised biomarker testing).

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. Independent of when the testing is performed (ie. at the time of disease progression or at initial diagnosis), if tissue is requested to be sent to a reference laboratory, source laboratories are required to retrieve and review slides and blocks before sending them on. The process of retrieving samples and sending them to reference laboratories currently may take between several days and two to three weeks. In an Australia study of 3688 colorectal cancer cases screened for mutations in the Kirsten rat sarcoma (KRAS) gene, more than 30% of cases took more than two weeks before the specimen was received by the testing laboratory (Scott RJ *et al.* 2014). The median turnaround time for the KRAS test was 17 days (range 0-191 days); 20% of cases took more than 4 weeks for a test result (Scott RJ *et al.* 2014).

At present the MBS reimburses five diagnostic tests (MBS item numbers 73332, 73336, 73337, 73338 and 73341) that can be performed on archived tissue samples and which are used to determine eligibility for co-dependent PBS medications. Several more applications for diagnostic tests are underway and there is expected to be more in future. This application refers substantially to the pathologist's time and expertise that is required to retrieve the archival tissue and perform the review. This application does not involve new technology; rather it relates to the medical expertise of the pathologists in assessing the adequacy of material; an investigational service which is currently unfunded.

The **retrieval** of tissue requires the pathologist to review pathology at the time of diagnosis or up to years after the original diagnosis to determine if an appropriate case is available and which exact biopsy if multiple or tissue block is appropriate to retrieve if there is more than one biopsy or block for a patient. The **review** of tissue by a trained pathologist involves:

- Verifying that the initial diagnosis of cancer was correct;
- Verifying that the correct diagnostic test has been ordered by the clinician;
- Assessing the adequacy of the material to ensure the requested test is able to be performed in the appropriate manner by determining -
    - the likely preservation of the tissue with regard to nucleic acid and protein degradation;
    - the presence of necrosis, inflammatory cell infiltrates, stroma, haemorrhage or pigmentation;
    - whether the absolute amount of tumour is adequate for testing.
- Determining the appropriate block of tissue to be sent from the correct tumour type and site and in the correct clinical context for testing, frequently from numerous tumour and other blocks (not infrequently > 20 in complex cases).

- When necessary, carrying out macro-dissection or micro-dissection of the tumour cells so that an appropriate sample is available for deoxyribonucleic acid (DNA) extraction. Some tests (eg., epidermal growth factor receptor (EGFR) testing) require a number of conditions for successful completion, including minimal sample size and proportion of tumour cells and artefacts of tissue preparation, which present particular challenges in the detection of somatic mutations.

- Ensuring preservation of material for future testing in keeping with laboratory quality standards.

Table 1 presents the steps involved in the review of archival tissue and whether the processes are currently funded or eligible for funding by the MBS.

Table 1: Steps in the review of archival tissue and whether they are currently funded or eligible for funding by the MBS

	Currently funded by the MBS?	Eligible for funding by the MBS?
Review of pathology records to select appropriate sample	No	Yes – Professional service
Assessment of preservation of tissue with regard to nucleic acid and protein degradation	No	Yes – Professional service
Assessment of the presence of necrosis, inflammatory cell infiltrates, stroma, haemorrhage or pigmentation	No	Yes – Professional service
Assessment of the amount of tissue	No	Yes – Professional service
Dissection and preparation of tissue	No	Yes – Professional service
Determination of appropriate block	No	Yes – Professional service
Preservation of tissue and return to archive	No	Yes –Professional service

MBS = Medicare Benefits Schedule

The majority of tissue retrieval and review is performed for patients following the progression of cancer. Cancers are characterised by genetic mutations, some of which can be targeted by specific therapies that improve patient outcome. Testing for these mutations ensures that those patients who will benefit from the relevant therapies are treated. Conversely, those who do not have the mutations are treated using different approaches, thus preventing the incorrect use of expensive and potentially harmful treatments. These tests are critical for best practice cancer treatment. Cancers also have a large heritable component and testing of tissues can identify patients with heritable cancers, thereby enabling appropriate prevention strategies to be employed.

Although it is cancer tissues that are predominantly reviewed to assess eligibility for PBS listed pharmaceuticals, archived non-cancerous tissue samples may occasionally be reviewed to aid in the diagnosis of genetic diseases.

Delivery of the intervention

The patient population that will predominantly benefit from the retrieval and review of archival tissue are patients with cancers that may be eligible for targeted treatments. The request to retrieve archival samples for testing will come from a specialist clinician. The requested tests will usually be biomarker tests that facilitate treatment selection and/or refine prognosis that were not requested at the time of the initial histological examination. The purpose of requesting MBS funding for the proposed investigational item is to ensure that these requests are able to be dealt with in a prompt timeframe and provide appropriate remuneration to the source laboratory for retrieving and reviewing tissue for testing. There is evidence that provision of a block retrieval fee significantly reduces the block retrieval time to the reference lab.

At present there are five pathology items listed on the MBS which are commonly used to select patients for targeted therapies which are available on the PBS.

- Testing for human epidermal growth factor receptor 2 (HER2) gene amplification for patients with breast cancer (item 73332 added to the MBS May 2012). HER2 testing is used to identify women with breast cancer suitable to be treated with trastuzumab. In most cases, this test occurs at the time of diagnosis however, in a small number of cases it is required retrospectively during the course of patient care eg for patients presenting with metastatic disease.

- Testing for the BRAF V600 gene mutation in patients with Stage III or Stage IV melanoma (item 73336 added to the MBS on December 2013). BRAF V600 mutation testing is used to identify a subgroup of patients with unresectable stage IIIc or metastatic stage IV cutaneous melanoma who are likely to benefit from treatment with dabrafenib.

- Epidermal growth factor receptor (EGFR) testing in patients with non-small cell lung cancer (item 73337 added to the MBS on January 2014). Clinical trial data show EGFR mutation status in patients diagnosed with Stage IIIb or Stage IV non-small cell lung cancer to be a crucial indicator of response to erlotinib and gefitinib. Patients with the mutation who are treated with these agents have a significant quality of life advantages and improvements in progression free survival over patients receiving platinum-based chemotherapy.

- Kirsten rat sarcoma (RAS) oncogene mutation testing in patients with Stage IV colorectal cancer (item 73338 added to the MBS on April 2014). RAS testing is used to identify patients with Stage IV colorectal cancer who are likely to benefit from second-line treatment with cetuximab or panitumumab.

- Anaplastic lymphoma kinase (*ALK*) immunoreactivity testing for patients with Stage IIIb or Stage IV non-squamous non-small cell lung cancer (item 73341 added to the MBS on July 2015) and who are negative for mutations of EGFR. This test is for selecting patients who may be treated with crizotinib.

The proposed MBS item is not limited to these five tests as more are being considered for listing currently and will continue to be considered in the future by MSAC. The MBS items associated with these biomarker tests are outlined in Table 2. Particular note should be made for the absence of retrieval and review of archival tissue when required for the specific testing.

Table 2: MBS item descriptors for biomarker tests currently listed on the MBS

Category 6 – PATHOLOGY SERVICES
MBS 73332 An in situ hybridization (ISH) test of tumour tissue from a patient with breast cancer requested by, or on the advice of, a specialist or consultant physician who manages the treatment of the patient to determine if the requirements relating to human epidermal growth factor receptor 2 (HER) gene amplification for access to trastuzumab under the Pharmaceutical Benefits Scheme (PBS) or the Herceptin Program are fulfilled. Fee: $315.40 Benefit: 75% = $236.55 85% = $268.10
Category 6 – PATHOLOGY SERVICES
MBS 73336 A test of tumour tissue from a patient with unresectable stage III or stage IV metastatic cutaneous melanoma, requested by, or on behalf of, a specialist or consultant physician, to determine if the requirements relating to BRAF V600 mutation status for access to dabrafenib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Fee: $230.95 Benefit: 75% = $173.25 85% = $196.35
Category 6 – PATHOLOGY SERVICES
MBS 73337 A test of tumour tissue from a patient diagnosed with non-small cell lung cancer, shown to have non-squamous histology or histology not otherwise not otherwise specified, requested by, or on behalf of, a specialist or consultant physician, to determine if the requirements relating to epidermal growth factor receptor (EGFR) gene status for access to erlotinib or gefitinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Fee: $397.35 Benefit: 75% = $298.05 85% = $337.75
Category 6 – PATHOLOGY SERVICES

MBS 73338

A test of tumour tissue from a patient with metastatic colorectal cancer (stage IV), requested by a specialist of consultant physician, to determine if the requirements relating to rat sarcoma oncogene (RAS) gene mutation status for access to cetuximab or panitumumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled, if:

(a) The test is conducted for all clinically relevant mutations on KRAS exons 2,3, and 4 and NRAS exons 2,3 and 4; or
(b) A RAS mutation is found.

Fee: $362.59 Benefit: 75% = $271.95 85% = $308.25

Item 73338 provides for testing of RAS mutations to limit subsidy of anti-EGFR antibodies to only those patients demonstrated to have no RAS mutations.

For a Medicare benefit to be payable, the test must be conducted for all clinically relevant mutations on KRAS exons 2,3 and 4 and NRAS exons 2,3, and 4, or until a RAS mutation is found.

Enabling the requirements of the item descriptor to be met once any RAS mutation is found means that once the test indicates that the patient is not RAS wild-type and therefore not suitable for access to cetuximab and panitumumab under the PBS, a pathologist is not required to continue testing for other clinically relevant mutations.

Category 6 – PATHOLOGY SERVICES

MBS 73341

Fluorescence in situ hybridisation (FISH) test of tumour tissue from a patient with locally advanced or metastatic non-small cell lung cancer, which is of non-squamous histology or histology not otherwise specified, with documented evidence of anaplastic lymphoma kinase (*ALK*) immunoreactivity by immunohistochemical (IHC) examination giving a staining intensity score > 0, and with documented absence of activating mutations of the epidermal growth factor receptor (*EGFR*) gene, requested by a specialist or consultant physician to determine if requirements relating to *ALK* gene rearrangement status for access to crizotinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

Fee: $400.00 Benefit: 75% = $300.00 85% = $340.00

Source: MBS online, www.mbsonline.gov.au
ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; FISH = fluorescence in situ hybridisation; IHC = immunohistochemical; KRAS = Kirsten rat sarcoma; MBS = Medicare Benefits Schedule; NRAS = neuroblastoma rat sarcoma; PBS = Pharmaceutical Benefits Scheme

Table 3 presents the incidence of the cancers in 2011 associated with each of the MBS approved pathology tests and the estimated number of each test performed using retrieved archival tissue in 2014.

Table 3: The estimated number of MBS approved biomarker tests performed in 2014 using retrieved tissue

Cancer type and biomarker	Cancer incidence 2011	% that have biomarker	Number of MBS funded tests 2014 [a]	% of tests performed on retrieved tissue [b]	Number of tests performed on retrieved tissue
Melanoma BRAF	11,570 [3]	45.8% [6]	1,126	~ 50%	565
Non-small cell lung EGFR	10,511 [4]	10-20% [7]	1,451	~ 30%	435
Colorectal KRAS	15,151 [5]	35-40% [8]	404	~ 80% *	325

Cancer type and biomarker	Cancer incidence 2011	% that have biomarker	Number of MBS funded tests 2014 [a]	% of tests performed on retrieved tissue [b]	Number of tests performed on retrieved tissue
Total			**2,981**		**1,325**

* According to the RCPA, KRAS testing requires tissue retrieval 'for the majority of cases' – this was assumed to be 80%, the proportion of patients who did not have metastatic disease at diagnosis.
AIHW = Australian Institute of Health and Welfare; DAP = decision analytic protocol; EGFR = epidermal growth factor receptor; KRAS = Kirsten rat sarcoma; MBS = Medicare Benefits Schedule; MSAC = Medical Services Advisory Committee; NSCLC = non-small cell lung cancer; RCPA = Royal College of Pathologists of Australasia
Additional sources:
a: Medicare statistics: www.humanservices.gov.au/corporate/statistical-information-and-data/medicare-statistics
b: Estimates provided from the RCPA

The total number of MBS funded biomarker tests that required the retrieval and review of archival tissue in 2014 was estimated to be 1,325. Approximately 50% of BRAF and 30% of EGFR tests require some form of tissue retrieval, either from the archives or from another laboratory. At present the majority of RAS tests are performed on retrieved tissue, for the purposes of the above calculation this was assumed to be 80%. The ALK gene mutation is estimated to occur in 3-5% of non-small cell lung cancer patients[9] but it can only be identified after testing the sample, not before retrieval of the sample

There are a number of other tests currently being considered by MSAC, from which a small number of patients would also benefit from tissue retrieval, including:

- 1172 – BRAF genetic testing to determine PBS access to vemurafenib (vemurafenib was deferred by the PBS in March 2013)
- 1342.1 – Oncotype DX® breast cancer assay to quantify the risk of disease recurrence and predict adjuvant chemotherapy benefit;
- 1407 – EGFR mutation testing to determine access to AZD9291 on the PBS in patients with non-small cell lung cancer; and
- 1408 – a prognostic RT-qPCR test for ER+ve/HER2-ve breast cancer.

It should be noted, however, that due to the changing biomarker profiles of some tumours, either due to previous treatment or inherent instability, for some biomarker tests, including some currently in the MSAC process, tissue obtained at a previous stage of disease will be unsuitable, and testing might require fresh tumour tissue.

Additionally, there are up to 8,000 known rare non-cancer diseases, the majority of which have a genetic origin. A small subset of these would benefit from the assistance of tissue retrieval eg FISH testing for specific diagnostic translocations. It is assumed that absolute numbers would be low.

Biomarker testing is generally only performed once per patient. The MSAC application for BRAF testing and vemurafenib (MSAC application #1172) identified that a small percentage

of patients (between 0.4% and 9.4%) would require a re-biopsy due to an inadequate amount of tumour tissue, poor quality of the sample, recurrences, or further mutations resulting in possible biomarker differences from the primary tumour. This concurs with expert opinion, which suggests that < 1% to approximately 10% of patients require re-biopsy depending on the tissue of origin. As with all medical procedures, there is a small risk associated with performing a biopsy, which varies according to the site of the primary tumour or metastasis, and which may increase with the deterioration of the patient's health.

Prerequisites

There are no prerequisites for the proposed investigational service as laboratories are required by law to retain archival tissue for 10 years. If, in the opinion of the referring specialist clinician, further testing of previous patient tissue samples will provide diagnostic or prognostic information that will affect healthcare outcomes, the pathologist will request the retrieval of archival tissue.

Co-administered and associated interventions

Although there are no co-dependent interventions associated with the retrieval and review of archival tissue, the process is closely associated with the MBS funded pathology tests outlined in Table 2 and their co-dependent administration of PBS medications. As stated above, it has been suggested that the item could be specified to be co-dependent with pharmacogenomics tests; however, this may not be appropriate as there are other conditions that warrant tissue retrieval.

Although the retrieval and review of archival tissue occurs presently in an unfunded capacity, MSAC is considering an increasing number of biomarker test proposals. If these tests receive MBS funding, the use of retrieved tissue samples will increase.

Listing proposed and options for MSAC consideration

Proposed MBS listing

The application seeks a new service with an MBS fee, as per Table 4. Once established, this item could become a sub-item in applications for funding of new genetic tests.

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Table 4: Proposed MBS item descriptor for the retrieval and review of archival pathology samples

Category 6 – PATHOLOGY SERVICES
MBS xxxxx 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

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 is proposed from the date of request. There should be only one retrieval per patient sample however 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. These activities take in the range of 10-30 minutes and include the assessment of the samples as set out in Table 5, representing a cost of approximately $50 to $120. Additionally, there are the administration costs associated with the retrieval from the archive (on-site or off-site) that are between $25 and $45. The actual cutting of the slides, which, although not always performed by the pathologist, is always performed by a skilled professional medical or scientific practitioner under the supervision of a pathologist, is part of the professional service and the cost is in the order of $10 to $40. These fees are outlined in Table 5. An indicative fee charged by one public sector provider is $150.

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Table 5: Steps in the review of tissue samples, and the fees requested by the RCPA

	Currently funded by the MBS?	Fee range estimated by RCPA
Review of pathology records to select appropriate sample	No	$25 to $45
Assessment of original diagnosis and type of test requested	No	$50 to $120
Assessment of preservation of tissue with regard to nucleic acid and protein degradation	No	
Assessment of the presence of necrosis, inflammatory cell infiltrates, stroma, haemorrhage or pigmentation	No	
Assessment of the amount of tissue	No	
Dissection and preparation of tissue	No	$10 to $40
Determination of appropriate block	No	
Preservation of tissue and return to archive	No – Legal requirement to archive tissue	-

MBS = Medicare Benefits Schedule; RCPA = Royal College of Pathologists of Australasia

Variations could include whether one or more samples of the tissue are requested at the same time. Additionally, the fee will be payable on more than one occasion if testing for different biomarkers is performed on different occasions.

Clinical place for proposed intervention

Figure 1 provides an outline of where the retrieval and review of archival tissue fits in the investigational algorithm.

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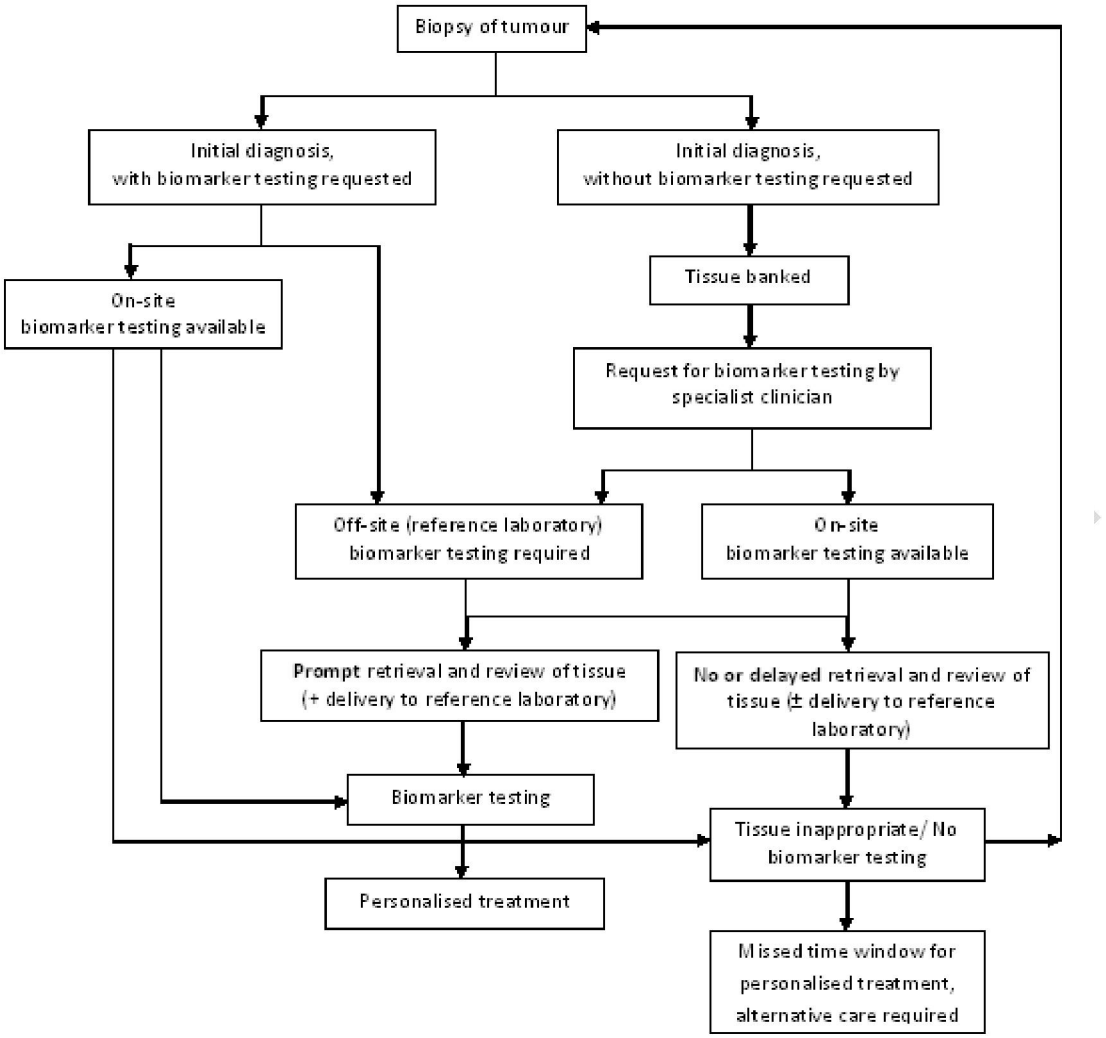
Figure 1: The investigational algorithm and the place of the retrieval and review of tissue samples



MBS = Medicare Benefits Schedule

There is no current MBS listing for the retrieval and review of archival tissue. It has been suggested that the lack of MBS funding currently results in pathologists providing the service with varying degrees of urgency. With MSAC considering the addition of new biomarker tests to the MBS to support the increasing availability of targeted cancer therapies, the requirement to review archival tissue in the future may also increase, which may make the current situation unsustainable.

There are many local and international clinical guidelines supporting the need for ancillary and additional testing on cancers to personalise care and optimise outcomes. Many of these have been previously analysed by MSAC in the process of approving the currently MBS listed biomarker tests.

Comparator

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

1. Retrieval of archived tissue without review by a pathologist; and
2. No retrieval of archival tissue (and no diagnostic testing), with or without the ability to acquire a new tissue sample.

The first comparator, retrieval without a pathologist review, would result in a high false positive and false negative rate with increased costs to the health system with repeat tests and inappropriate use of targeted therapy which may be detrimental to patient care and cost to the health system eg recent data suggests that treating patients whose tumours have RAS mutations with EGFR monoclonal antibodies result in an adverse outcome.

The second comparator reflects the situation of the retrieval/review occurring too late or not at all, with the ordering clinician required to make a treatment decision in the absence of the test result or the patient undergoing a repeat procedure at significant cost and suffering. A number of such procedures, such as lung biopsy, are associated with significant patient risk (eg pneumothorax) with an associated hospital stay which has a cost burden on the health care system. With MBS funding it is expected that the service will be prioritised, resulting in more prompt diagnoses for patients and optimal patient care.

Outcomes for safety and effectiveness evaluation

Patients with advanced malignancy often have very limited options, and rapid decision-making regarding optimal therapy is needed. The proposed MBS item is intended to facilitate the rapid referral of appropriate material for critical testing and thus result in improved treatment and disease outcomes.

Suitable evidence on the benefits of the proposed MBS item for patients or health professionals may need to take the form of clinical audits. The applicant is involved in quality assurance programs and studies that will form the basis of these indicators of evidence in support of the assessment phase (Cooper *et al.* 2014, Scott RJ *et al.* 2014).

The outcomes upon which the clinical performance of MBS funded retrieval and selection of archived tissue samples to be assessed include:

1. test turnaround times;
2. tests not done or too late;
3. biopsies and other investigations avoided;

4. clinical errors avoided;
5. unnecessary testing or tissue retrieval from the patient; and
6. pathologist agreement in diagnosis.

These represent intermediate or surrogate outcomes for subsequent optimal patient management.

Summary of the modified PICO to be used for assessment of evidence

Table 6 provides a summary of the modified PICO used to:

(1) define the patients, intervention and comparator; and

(2) outline the potential outcomes of MBS funded retrieval and review of archival tissue by a pathologist.

Table 6: Summary of modified PICO

Patients	Intervention	Comparator	Potential outcomes
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.	MBS funding of the retrieval and review of archived tissues and selection of appropriate samples for further pathological testing	1. Retrieval and no review of archived tissues; 2. No retrieval or review of archived tissue with new sample required	**Change in management** • test turnaround times; • tests not done or too late; • biopsies and other investigations avoided; • clinical errors avoided; • unnecessary testing or tissue retrieval from the patient; and • pathologist agreement in diagnosis. - **Cost impact** - Cost-effectiveness analysis - Reduced costs for patients; - Increased costs for the MBS

Questions

1. **What is the total number of services for retrieval and review of archival tissue expected?**
2. **What is the current median turnaround time from ordering a test and receiving the test result?**
3. **Would more prompt diagnoses occur if MBS funded the proposed service?** 29 days to 11 days after implementation of retrieval fee within 2 months, further reduction expected **Is there a difference in the time taken in to provide a biomarker test result in laboratories that charge for the retrieval and review of archival tissue compared to in those that do not?**
4. **What are the cost and care consequences if the status quo remains?**
5. **Is it possible to measure improved patient outcomes?**

MBS = Medicare Benefits Schedule; PICO = patient, intervention, comparator, outcome

Clinical claim

The purpose of the proposal is to incentivise pathologists to prioritise the review and referral of archival material for specialised testing upon request. The outcome is expected to be faster compliance with requests which may result in improved patient care. It is assumed that MBS funding will also improve equity of patient access to this investigational service. It

is suggested that sustainable long term access to tissue archives is essential for individual patient and population improvement in health care outcomes.

As the proposed investigational service supports the clinical claim of improved patient care, the use of cost-effectiveness or cost-utility analyses is appropriate. A assessment of the financial impact to the MBS and patients of the retrieval and review of archival tissue is also appropriate.

Outcomes and health care resources affected by introduction of proposed intervention

Outcomes for economic evaluation

The outcomes upon which the economic analysis of MBS funded versus no retrieval and/or review of archival tissue by a pathologist could be evaluated are:

- Cost per quality-adjusted life years (incorporating full patient treatment pathway over time);
- Cost to the MBS (if MBS funding of the proposal is supported); and
- Costs to patients (if MBS funding of the proposal is not supported).

Health care resources

Table 7 provides a summary of the healthcare resources that should be considered in the financial analysis of the retrieval and review of archival tissue by a pathologist.

Table 7: List of resources to be considered in the financial analysis

-	- Provider of resource	- Setting in which resource is provided	- Proportion of patients receiving resource	- Units of resource per time horizon per patient	- Unit costs MBS	- Safety nets*	- Other govt budget	- Private health insurer	- Patient	- Total cost
Resources to deliver: Proposed intervention	-	-	-	-	-	-	-	-	-	-
MBS funded retrieval and review of archived tissue for testing of: - BRAF V600 - EGFR - RAS - Other biomarkers^	Pathologist	Pathology laboratory	 50% 30% 80% ?%	 1 1 1 1	$85 to $205	-	-	-	-	-
Resources to deliver: Comparator	-	-	-	-	-	-	-	-	-	-

-	- Provider of resource	- Setting in which resource is provided	- Proportion of patients receiving resource	- Units of resource per time horizon per patient	- MBS	- Safety nets*	Unit costs Other govt budget	Private health insurer	- Patient	- Total cost
Unfunded retrieval and review of archived tissue for testing of: - BRAF V600 - EGFR - RAS - Other biomarkers^	Pathologist	Pathology laboratory	 50% 30% 80% ?%	 1 1 1 1	-	-	-	-	$0 to $175	-

* Include costs relating to both the standard and extended safety net
^ Includes biomarker tests currently being considered by MSAC and those related to non-cancerous diseases
EGFR = epidermal growth factor receptor; govt = government; RAS = rat sarcoma; MBS = Medicare Benefits Schedule

Proposed structure of financial impact of MBS funding

It is proposed that the assessment report presents an economic evaluation and financial assessment of tissue retrieval and review. A combination of expert opinion, audit data from laboratories and data from the literature may be used to estimate the incidence of tissue retrieval. The financial impact of funding or not funding the investigational service to the MBS and to patients will also be provided.

Figure 2 provides a draft structure for the economic evaluation.

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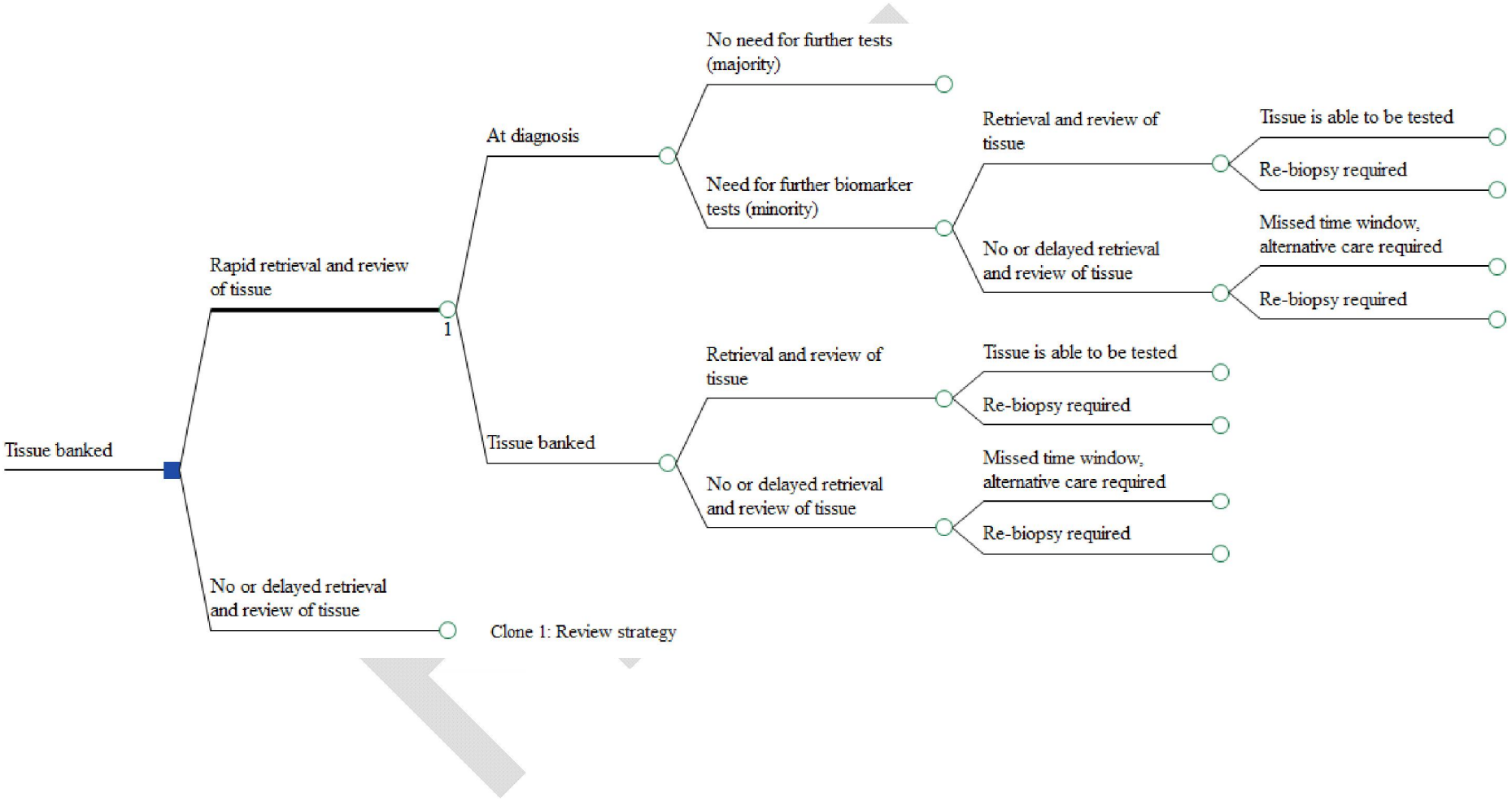
Figure 2: Draft structure of the decision tree for the proposed intervention



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