The retrieval and review of archival tissue by pathologists for further diagnostic testing

October 2016

MSAC application no. 1331.1

Assessment report

CONTENTS

TABLES

BOXES

FIGURES

ACRONYMS AND ABBREVIATIONS

ACIM	Australian Cancer Incidence and Mortality
AE	Adverse event
ALK	Anaplastic lymphoma kinase
BSC	Best supportive care
CE	Cost-effectiveness
CIMP	CpG island methylator phenotype
CISH	chromogenic in situ hybridisation
CRC	colorectal cancer
DAP	Decision Analytic Protocol
DNA	Deoxyribonucleic acid
EGFR	Epidermal growth factor receptor
EGRF	Epidermal growth factor
EQA	External quality assessment
FFPE	Formalin-fixed paraffin-embedded
FISH	fluorescence in situ hybridisation
HER2	human epidermal growth factor receptor 2
HESP	Health Expert Standing Panel
IB	Incremental benefit
IC	Incremental cost
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry
IQR	Interquartile range
ISH	in situ hybridisation
KRAS	Kirsten rat sarcoma
MSAC	Medical Services Advisory Committee
NICE	National Institute for Health and Care Excellence
NSCLC	Non-small cell lung cancer
PASC	Protocol Advisory Sub-Committee
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PCR	Polymerase chain reaction
PFS	Progression free survival
PSD	Public Summary Documents
RCPA	The Royal College of Pathologists of Australasia

ACIM	Australian Cancer Incidence and Mortality
RT	Real time
QALY	Quality adjusted life years
QoL	Quality of life
SPA	Special Pricing Arrangements
TAT	Turnaround time
TATO	Overall turnaround time
TATRR	Time from receipt of sample at test facility to reporting of test result
TATRS	Time from ordering of test to receipt of sample

EXECUTIVE SUMMARY

MAIN ISSUES FOR MEDICAL SERVICES ADVISORY COMMITTEE (MSAC) CONSIDERATION

- The review of archival tissue samples prior to diagnostic testing is widely disseminated in clinical practice. As such, there is no real evidence for the clinical utility of the review process.
- A substantial proportion of samples (approximately 60%) are not retrieved, reviewed and delivered to the testing laboratory within one week as mandated by the proposed Medicare Benefits Schedule (MBS) item descriptor. The extent to which remuneration via the MBS will improve this proportion could not be quantified.
- MSAC may wish to consider how the requirement for the sample to be delivered to the testing laboratory within seven days is to be enforced.
- The requested fee for the proposed service is $150. The reimbursed fee for a similar service in the United States is lower. In the 2013 the Medicare Physician Fee Schedule, national reimbursement for code 88363 was US$19.39 (facility) to US$56.82 (non-facility). In 2016, the non-facility fee is US$23.97.
- Assuming funded retrieve and review will increase the number of samples being reviewed within seven days, the cost-effectiveness of funded retrieve and review (vs current practice) is intrinsically linked to the cost-effectiveness of the co-dependent treatment. This is because the faster processing time will mean more eligible patients being initiated on treatment.
- Other comparisons, including retrieval without review, requested by PASC are equally hypothetical. The evidence shows a proportion of retrieved archival tissues are sub-optimal for testing. It is likely test failure rates would increase if tests were performed on unreviewed samples. However, the extent to which this could happen is unknowable, given the available evidence reflects the circumstance where all samples are reviewed.
- As such, MSAC could consider the extent to which health technology assessment is the appropriate mechanism by which to determine whether this service should be included on the MBS. Assuming this retrieve 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.
- Therefore, this assessment report considers the cost-effectiveness of co-dependent technologies whilst allowing for the additional cost of funding the retrieve and review process. This scenario reflects the original co-dependent application for cetuximab in the treatment of metastatic colorectal cancer. Including the cost of the retrieve and review process has the impact of increasing the incremental cost-effectiveness ratio of the co-dependent technologies versus best supportive care from $60,000 to $67,247 per QALY.
- This cost-effectiveness scenario reflects only a single application of the retrieve and review process. Nevertheless, this result may have application to other oncology type co-dependent technologies with similar treatment costs and cost-effectiveness. However, the extent to which this retrieve and review process is necessary, effective or cost-effective in applications other than pharmacogenetic tests remains uncertain.
- The financial implications of the proposed service to the MBS are subject to uncertainty because the range of tests to which the service could be applied may expand in the future.
- In future, financial and cost-effectiveness uncertainty of this service in additional testing applications could be managed by incorporating the cost of this service into the fee for the test itself.

This contracted assessment examines the evidence to the support listing of 'the retrieval and review of archival tissue by pathologists for further diagnostic testing' on the Medicare Benefits Schedule

(MBS). The service would be exclusively used for the management of patients who have conditions which may benefit from further testing of previously biopsied archived tissue. The target population comprises mainly, although not exclusively, patients who have cancer conditions which may benefit from current MBS funded tests for assessing eligibility for PBS funded co-dependent therapies. The overriding claim made by the applicant 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.

ALIGNMENT WITH AGREED DECISION ANALYTIC PROTOCOL

This contracted assessment of the proposed service addresses most of the Population, Intervention, Comparator and Outcomes (PICO) elements that were pre-specified in the Decision Analytic Protocol (DAP) that was ratified by Protocol Advisory Sub-Committee (PASC). Deviations from the DAP in are summarised and justified in Table 1. The main departures relate to the patient population and the comparators considered in the assessment.

Table 1 PICO items which deviate from the 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 of 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 BSC); 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 in to two comparators (No retrieval and patient referred directly for biopsy; No retrieval, no test, and patient remains ineligible for PBS drug).
Relevant Section	Section A1.1; Section A.4; Section B; Section D	Section A.1.2; Section A.5; Section D

PROPOSED MEDICAL SERVICE

The proposed service is for the retrieval and review of archival tissue by a pathologist to determine the appropriate tissue samples for further diagnostic testing. Reimbursement is intended only if the service is completed within a 7-day time period. The proposed service will mainly, although not exclusively, be used for assessing a cancer patient's eligibility to receive targeted therapy listed on

the Pharmaceutical Benefits Scheme (PBS) or identifying patients who may be suitable for clinical trials of new therapies. While the review of archival tissue prior to further diagnostic testing is generally accepted practice (PASC Outcomes on Protocol 1331), there is currently no formal arrangement for public or private reimbursement for this service by a pathologist in Australia.

PROPOSAL FOR PUBLIC FUNDING

The proposed MBS item descriptor is summarised in Table 9.

Table 2 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

POPULATION

The proposed population for the service comprises patients who have conditions which may benefit from further testing of previously biopsied archived tissue. A base case estimate, based on MBS utilisation data for tests for assessing eligibility for co-dependent PBS funded cancer therapies, suggests the total number of service episodes for the proposed service to be approximately 7,400 per year. However, it is important to note the proposed MBS item will not necessarily be limited to these six test items as more co-dependent treatments and associated diagnostic tests become available. Furthermore, there may be tests currently listed on the MBS other than the pharmacogenetics tests examined in this assessment to which this service may apply.

COMPARATOR DETAILS

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

- 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])
- Retrieval and review by a pathologist without reimbursement (current practice)

The first three comparators 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 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 (PASC Outcomes on Protocol 1331).

CLINICAL MANAGEMENT ALGORITHM(S)

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.

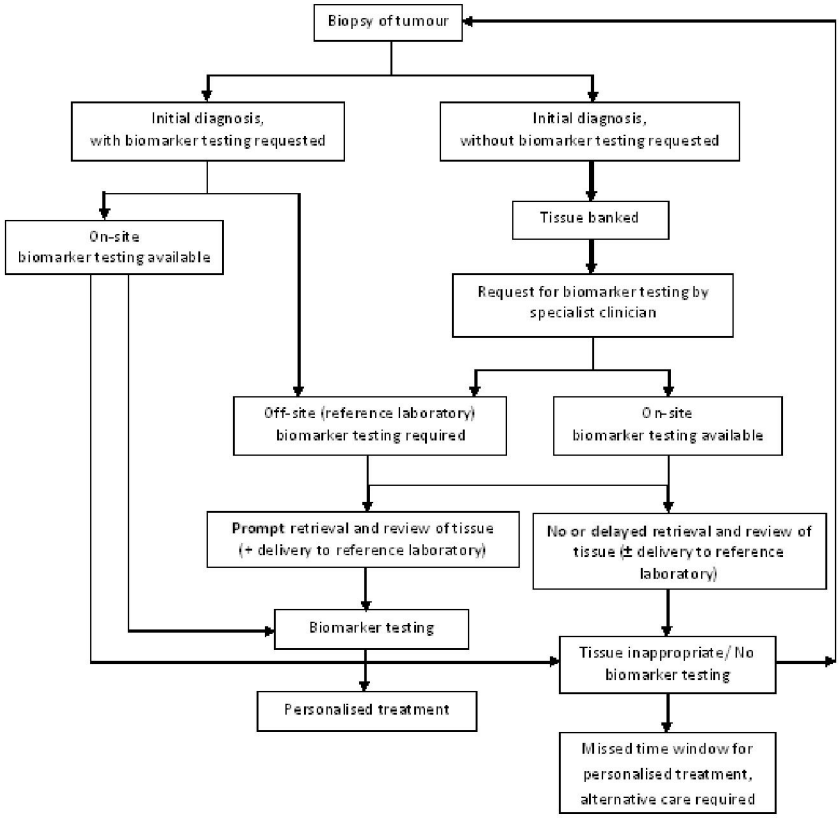

Figure 1 The investigational algorithm and the place of the retrieval and review of tissue samples

KEY DIFFERENCES IN THE DELIVERY OF THE PROPOSED MEDICAL SERVICE AND THE MAIN COMPARATOR

The retrieve and review intervention is accepted and standard practice prior to the diagnostic testing of archival tissue rather than a new intervention. The proposed service item means the intervention will be reimbursed if it is completed within 7 days. The implications of this are discussed further in the clinical claim section.

CLINICAL CLAIM

The overriding claim made in the DAP 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. The purpose of the economic model is therefore to quantify the cost and quality of life implications of this improved turnaround time. As such, the form of economic evaluation is cost-utility analysis.

Given the retrieval and review of archival tissues is already generally accepted, the remaining comparisons in the assessment are considered hypothetical. In each case the retrieve and review intervention is assumed superior because:

- Compared to retrieval without review:
    - Retrieve and review should reduce the number of tests being conducted on sub-optimal tissue which in turn would reduce costs on futile tests and/or improve diagnostic accuracy
- Compared to no retrieval and patient referred directly for biopsy:
    - Retrieve and review has time, cost and quality of life advantages for the patient
- Compared to no retrieval, no test, and patient remains ineligible for PBS drug:
    - Retrieve and review means those patients who would be eligible for the PBS drug go on to receive the efficacy, effectiveness and QALY gains associated with the PBS treatment

As such, cost-utility analysis is the appropriate form of economic evaluation relative to each of the four comparators.

APPROACH TAKEN TO THE EVIDENCE ASSESSMENT

In the absence of direct data, a linked evidence approach was required (Figure 4). The objective was to collect and link evidence 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. MEDLINE and EMBASE electronic literature searches were conducted to identify evidence regarding the process of molecular diagnostic testing in clinical practice with a focus on test success or failure and test turnaround times. The systematic literature review focused on of patients who have cancer conditions which may benefit from current MBS funded tests for assessing eligibility for PBS funded co-dependent therapies. Further linked evidence regarding test diagnostic performance, survival outcomes and incremental costs and benefits of receiving targeted therapy compared to standard therapy according to tumour genotype relied on information available in relevant MSAC and PBAC public summary documents (PSDs) relating to molecular diagnostic tests listed on the MBS and associated co-dependent therapies listed on the PBS.

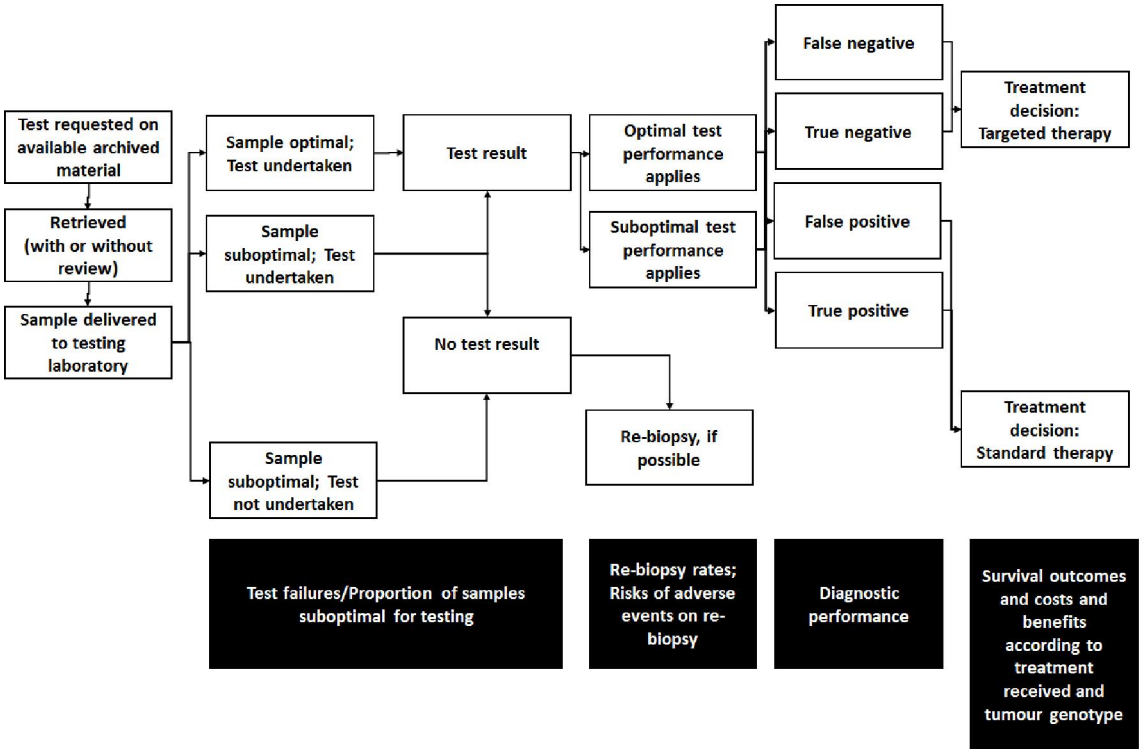

Figure 2 Outline of linked evidence approach

CHARACTERISTICS OF THE EVIDENCE BASE

The electronic literature searches identified a total of 27 unique studies describing diagnostic testing undertaken either as a requested service or as routine in clinical practice for the management of patients and where the testing involved one or more of the five molecular diagnostic tests currently listed as items on the MBS to select patients for targeted cancer therapies available on the PBS. More than half of the information sources were confined to conference abstracts, and consequently limited in detail. The database included multi-national, national, regional and single institution and retrospective, retro-prospective and cross-sectional studies. The publication dates ranged from 2009 to 2016. The testing periods reported upon ranged from 2008 to 2015. Studies were from Australia (1), Belgium (1) Brazil (1), Canada (3), France (6), Spain (2) UK (5), and the US (6) and two studies were multi-national (Europe; Asia/Europe/Latin America). Information sources were inconsistent in specifying whether the tissues tested were necessarily archival FFPE tissue.

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 collections. As such the data are not amenable to any meaningful pooling.

The available data do not compare between scenarios which do and do not include the review process. Nonetheless, in general terms, the data do provide an indication of the technical outcomes of the testing procedure that may be "worsened" should proposed service involving the review of archival samples prior to testing not be undertaken or not adequately reimbursed.

RESULTS

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 most attributed to a delay in when the sample was received 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 a tissue was unavailable for testing due the sample not being retrievable from the archive or, the tissue was retrievable but upon review, considered sub-optimal 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, however, on subsequent analysis the sample has failed to yield an interpretable result ranged from 0.3% to 16%, with the majority of studies recording between 0.3% and 3.0%. Taken together, these data confirm prior review by a pathologist identifies a proportion of archival tissues as being sub-optimal for molecular diagnostic testing. However, a proportion of archival tissues, which are deemed as suitable for testing, will 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.

TRANSLATION ISSUES

The main purpose of the economic model is to quantify the cost and quality of life implications of improved turnaround time (assuming all else remains equal) which will occur should funding for retrieval and review be included on the MBS. However, the main difficulty in the economic evaluation of retrieve and review relative to the alternative comparators is not the therapeutic claims of superiority but rather the magnitude of this superiority claim. For example, the proportion of the 60% of cases which currently take more than 7 days which will now take less than 7 days remains uncertain. To this end, the economic model relies on sensitivity analysis and threshold analysis to provide insight in to the extent of superiority required for the proposed retrieve and review item number to be deemed cost-effective.

APPLICABILITY

With the exception of data reported by Scott et al 2014 in relation to test turnaround times for KRAS testing in mCRC, the applicability of the data presented to the Australian setting cannot be ascertained or guaranteed. Any formal data applicability assessment is considered infeasible.

EXTRAPOLATION

The clinical evaluation covers a time period up until the test result is obtained. Therefore, there are no specific time-related extrapolation issues to consider in a pre-modelling study.

TRANSFORMATION

The transformation issues in the economic evaluation follow the linked evidence framework (Table 3). That is, the implication of an absence of a review may lead to the potential for futile or inaccurate testing, or the implications for delayed testing may lead to the potential for disease progression before treatment can be initiated.

Table 3 Summary of links/transformations in the economic model

Alternative	Benefits of funded retrieval and review of sample	Transformation issue
Unfunded retrieve and review	Increases the number of samples reviewed within one week	Time savings lead to fewer "false negatives" because patients will be allocated to treatment in time (i.e. before disease progression)
Retrieve and no review of tissue sample	Reduces the number of tests being conducted on sub-optimal tissue (sample quality)	Cost savings Time savings
	Improves diagnostic accuracy and treatment allocation	Fewer false positives (more true negatives) leads to: Cost savings (drug avoided) QoL gains (toxicity avoided) Fewer false negatives (more true positives) leads to: Additional costs (drug used) QoL gains (drug efficacy)
No retrieval and patient referred directly for biopsy	Reduces the number of biopsies being conducted	Cost savings QoL gains from biopsies avoided
No retrieval and no new biopsy, no test	Patient remains ineligible for PBS drug and receives BSC. Patients who were truly eligible, but could not be identified because there was no retrieval or no new biopsy and therefore couldn't have the diagnostic test, will forgo any potential QALYs gained.	More true positives Additional costs (drug used) QoL gains (drug efficacy)

For the purposes of the economic evaluation a single population indication is used; mCRC. The listing of cetuximab as monotherapy or in combination with irinotecan based therapy (also BSC), following failure of first-line chemotherapy for treatment of patients with K-RAS wild-type metastatic colorectal cancer (mCRC) was recommended by the PBAC (PBAC PSD July 2010).

ECONOMIC EVALUATION

OVERVIEW

The clinical evaluation in Section B showed turnaround times for archived sample retrieval and review in current practice to be greater than 7 days in over 60% of cases (Scott et al. 2014). The proposed intervention requires this turnaround time to be less than seven days otherwise, the MBS fee is not payable.

Therefore, the purpose of the economic model is to quantify the cost and quality of life implications of this improved turnaround time. As such, the form of economic evaluation is cost-utility analysis.

MODEL STRUCTURE AND INPUTS

The economic evaluation is a modelled economic evaluation based on the data presented in Section B of this assessment report. The main purpose of the economic model is to quantify the cost and quality of life implications of improved turnaround time (assuming all else remains equal) which should occur if funding for retrieval and review was to be included on the MBS.

The decision analytic economic model follows a linked evidence approach and is structured to capture the impact of:

- improved retrieve 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
- the costs and outcomes of downstream treatment allocation decisions

A summary of the key characteristics of the modelled economic evaluation is given in Table 4.

Table 4 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) are 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

Due to the fact review of samples is widely disseminated in to clinical practice it was not possible to quantify the superiority of funded retrieve and review relative to the comparators. As such, the model uses hypothetical values to reflect the impact of the proposed funding, each of which are explored in sensitivity analysis. Key assumptions which quantify differences between funded retrieve and review and the comparators in a base case analysis are as follows:

For the purposes of defining a base case in the economic evaluation it will be assumed **all** of the 62% of retrieve and review processes that are not currently taking place within 7 days will do so in the arm of the model where MBS funding is provided.

Data from Section B estimates, for a world in which reviews do take place, 8.3% of samples will not yield a usable test results. The extent to which this variable would be altered should no review be undertaken is hypothetical and tested in sensitivity analysis. For the purposes of describing a base case analysis it is assumed the review process decreases the 8.3% figure by 5%. That is, 13.3% of cases will not yield a test result in the no review arm of the model.

The extent to which an unreviewed sample could or would compromise test accuracy is again a hypothetical value tested in sensitivity analysis of the model. The economic model describes sensitivity and specificity in relation to the patient's eligibility for PBS subsidised treatment. That is, a positive result means the patient is eligible for treatment. For the purposes of establishing a base case analysis a specificity for unreviewed samples of 95% is used. The sensitivity of unreviewed samples is 100%.

RESULTS

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 the table below.

Table 5 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 retrieve and review dominates retrieve without review and biopsy, due to higher costs from additional tests, biopsies and inappropriate treatment allocation based on a futile 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 retrieve 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 retrieve and review remained dominant compared to either no review or to 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 retrieve 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 retrieve 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.

ESTIMATED EXTENT OF USE AND FINANCIAL IMPLICATIONS

The financial implications to the MBS resulting from the proposed listing are summarised in Table 6.

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 pharmacogenetics 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 as a consequence of funded retrieve and review are not estimated due to inherent uncertainties associated with the proposed service's impact on downstream treatment practices and outcomes.

Table 6 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

SECTION A: CONTEXT

This contracted assessment of 'the retrieval and review of archival tissue by pathologists for further diagnostic testing', hereon referred to as the proposed service, is intended for the Medical Services Advisory Committee (MSAC). MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Schedule (MBS) in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

THEMA Consulting Pty. Ltd. has been commissioned by the Australian Government Department of Health to conduct a systematic literature review and economic evaluation of the proposed service. This assessment has been undertaken in order to inform MSAC's decision-making regarding whether the proposed medical service should be publicly funded.

Appendix A provides a list of the people involved in the development of this assessment report, including clinical expertise sourced from The Royal College of Pathologists of Australasia (RCPA)

The proposed use of the service in clinical practice was outlined in the Decision Analytic Protocol (DAP) that was presented to, and accepted by Protocol Advisory Sub-Committee (PASC). The DAP was released for public comment in October 2015.

A.1 ITEMS IN THE AGREED DAP

This contracted assessment of the proposed service addresses most of the PICO elements that were pre-specified in the DAP. Table 7 provides a summary of how the approach in the assessment conforms to the DAP, with any differences or changes justified. The main departures from the DAP relate to the patient population and the comparators considered in the assessment.

A1.1 PATIENT POPULATION

While there is a variety of other clinical scenarios that warrant tissue retrieval, this contracted assessment considers the proposed retrieve and review service within the context of assessing the suitability of a tissue sample for MBS funded diagnostic testing to determine a patient's eligibility for targeted cancer therapy on the PBS. 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 economic analysis focuses on patients with mCRC who may benefit from KRAS mutation analysis of previously biopsied archived tissue. The economic analysis relies on a linked evidence approach and the available evidence to inform the modelling was richest in this population.

A1.2 COMPARATORS

The first three comparators included 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 in to two comparators (No retrieval and patient referred directly for biopsy; No retrieval, no test, and patient remains ineligible for PBS drug).

A further comparator “unfunded retrieval and review” has been included in the assessment because “PASC considered that the proposed comparator of unfunded retrieval and review of archived tissues would be appropriate in considering the likely impact of public funding on service delivery” (PASC Outcomes on Protocol 1331).

Table 7 Items in the DAP and how addressed in the Assessment Report

PICO element	Patients	Intervention	Comparator	Potential outcomes
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.	MBS funding of the retrieval and review of archived tissues and selection of appropriate samples for further pathological testing	• 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	**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
Approach taken in the assessment	The systematic literature review focuses on of patients who have cancer conditions which may benefit from current MBS funded tests om 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.	Same as stated in the DAP	• 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 BSC) • Retrieval and review by a pathologist without reimbursement (current practice) 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 in to two comparators (No retrieval and patient referred directly for biopsy; No retrieval, no test, and patient remains ineligible for PBS drug)	The assessment reports on each of the outcomes specified in the DAP with the exception of 'pathologist agreement in diagnosis'. No data were reported on this outcome in the identified evidence base.

Table 8 provides a summary of research questions posed in the DAP, and where and how adequately they have been answered in the assessment.

Table 8 Research questions posed in the DAP and how addressed in the Assessment Report

Question	Summary of answer	Location in assessment report
What is the total number of services for retrieval and review of archival tissue expected?	The assessment report estimates the total number of pathology test services that could potentially be assisted by the proposed service to be approximately 29,000 per year in the next five years. When combined, less than a third of these tests are estimated to be performed on archive tissue. Therefore, the total utilisation of the proposed service is estimated to be approximately 7,400 per year.	Section E
What is the current median turnaround time from ordering a test and receiving the test result? Would more prompt diagnoses occur if MBS funded the proposed service?	The clinical evaluation in Section B showed turnaround times for archived sample retrieval and review in current practice in Australia to be greater than 7 days in over 60% of cases (Scott et al.2014). The proposed intervention requires this turnaround time to be less than seven days otherwise, the MBS fee is not payable. Assuming at least some laboratories currently taking longer than 7 days will respond to the reimbursement incentive provided by the MBS fee then, the proposed intervention is superior to the main comparator in terms of time taken for an optimal sample to be available for testing.	Section B
What are the cost and care consequences if the status quo remains?	Without direct evidence confirming as such, the proposed intervention can nevertheless be assumed to be superior to each one of the comparators on at least one outcome as follows: Compared to retrieval without review: • Retrieve and review should reduce the number of tests being conducted on sub-optimal tissue which in turn would reduce costs on futile tests and/or improve diagnostic accuracy Compared to no retrieval and patient referred directly for biopsy: • Retrieve and review has time, cost and quality of life advantages for the patient Compared to no retrieval, no test, and patient remains ineligible for PBS drug: • Retrieve and review means those patients who would be eligible for the PBS drug go on to receive the efficacy, effectiveness and QALY gains associated with the PBS treatment	Section D
Is it possible to measure improved patient outcomes?	Improved patient outcomes can be inferred via a linked evidence approach. The linked evidence approach is described in Section B2 and quantified in the economic evaluation in Section D.	Section B1, B2 and Section D

A.2 PROPOSED SERVICE

The proposed service is for the retrieval and review of archival tissue by a pathologist to determine the appropriate tissue samples for further diagnostic testing. The main purpose of pathologist review would be to ensure that sufficient tissue was available to perform the test. The proposed service is intended only to be reimbursed if it is completed within a 7-day time period.

While there is a variety of other clinical scenarios that warrant tissue retrieval and which are vital to patient care, the retrieval of tissues is primarily to assess a cancer patient's suitability for new, targeted drugs which are listed on the PBS or identifying patients who may be eligible for clinical trials of new therapies. The scope of the contracted assessment is limited to the oncology context.

BACKGROUND

Anatomical pathology tissue is any tissue that is biopsied or cut from a patient and excludes blood tissues. By law, pathology laboratories must retain anatomical pathology samples for 10 years, in case review or further diagnostic testing is required.

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.

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.

Accordingly, pathologists are increasingly retrieving and reviewing banked tissue, mainly 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 (MacDonald et al, 2011).

CURRENT FUNDING ARRANGEMENTS

Review of archival tissue prior to further diagnostic testing is generally accepted practice (PASC Outcomes on Protocol 1331). However, there is currently no formal arrangement for public or private reimbursement for this service by a pathologist in Australia.

The authors of the DAP indicate some laboratories absorb the costs of the retrieve and review service, but an increasing number of laboratories are charging patients (up to $175). The DAP further indicates there is evidence, anecdotal or otherwise, to suggest the lack of funding results in delays in tissue retrieval which, in turn, delays appropriate treatment and may result in sub-optimal patient cares. This may be leading to considerable inequity between patients who often have secondary or

advanced cancers.

THE INTERVENTION

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

The legal requirement for the retention of anatomical pathology samples for a minimum of 10 years means the accumulation of many tissue samples and archiving of these tissues is frequently 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). Independent of when the testing is performed (i.e., 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 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 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 the following

- 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 (e.g., 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.

A.3 PROPOSAL FOR PUBLIC FUNDING

The proposed MBS item descriptor is summarised in Table 9.

Table 9 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% = $112.50

Abbreviations: MBS; Medicare Benefits Schedule

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 as defined under the Health Insurance Act 1973. According to this 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.

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. The RCPA suggest these activities take in the range of 10-30 minutes and include the assessment of the samples as set out in Table 10, 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) estimated by the RCPA to be 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 has been estimated by the RCPA to be in the order of $10 to $40. These fees are outlined in Table 10. An indicative fee charged by one public sector provider is $150.

Table 10 Steps in the review of tissue samples, and the fees requested by the RCPA

Item of service	Currently funded by the MBS?	Fee range estimated by the RCPA
Review of pathology records to select appropriate sample	No	$25-45
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	NA

INTERNATIONAL FEE INFORMATION

The assessment notes a similar Medicare service in the United States (CPT Code 88363; introduced in 2011) for the "Examination and selection of retrieved archival (i.e., previously diagnosed) tissue(s) for molecular analysis (e.g., KRAS mutational analysis)".

The professional work of the pathologist that is covered by code 88363 appears similar to that of the proposed service in that it primarily consists of (1) retrieving the archive case report, blocks, and slides from storage; (2) re-examining the original report and slides to determine which block(s) contains cells that conform to the specifications of the requested molecular test; and (3) initiating preparation of the appropriate block(s) for referral to the molecular lab (www.apsmedbill.com). In contrast to the proposed service, no time limit for service completion appears to have been imposed in the US Medicare service.

In the 2013 the Medicare Physician Fee Schedule, national reimbursement for code 88363 was US$19.39 (facility) to US$56.82 (non-facility). By 2016, the non-facility fee was $23.97 (www.cap.org).

A.4 PROPOSED POPULATION

The proposed population for the service comprises patients who have conditions which may benefit from further testing of previously biopsied archived tissue. No official statistics are available regarding the frequency of the retrieval and review of archival tissue. However, given the patient population that will predominantly benefit from the service are patients with cancers that may be eligible for targeted treatments, an estimate of the number of patients benefiting from the service may be based on available MBS data regarding the utilisation of the currently funded tests for assessing eligibility for co-dependent therapies, as summarised in Table 11 below. Many of these tests were only recently added to the MBS listing. This means there exists limited longitudinal MBS statistics available for their usage.

Table 11 Pathology tests currently available on the MBS that are potentially relevant to the proposed retrieval and review of archival tissue by a pathologist

MBS item code	Examined gene and indication	Treatment administered	Annual incidence of the treated cancer in 2012, any disease stages
73332 (available on the MBS since May 2012)	Human epidermal growth factor receptor 2 (HER2) in women with breast cancer[a]	Trastuzumab	15,166[b]
73336 (available on the MBS since December 2013)	BRAF V600 gene mutation in patients with unresectable stage IIIc or metastatic stage IV cutaneous melanoma	Dabrafenib	12,036[b]
73337 (available on the MBS since January 2014)	Epidermal growth factor receptor (EGFR) testing in patients with Stage IIIb or Stage IV non-squamous non-small cell lung cancer	Erlotinib and gefitinib	5,791[c]
73338 (available on the MBS since April 2014)	Rat sarcoma (RAS) oncogene mutation testing in patients with Stage IV colorectal cancer	Cetuximab or panitumumab	14,958[b]
73341 (available on the MBS since July 2015)	Anaplastic lymphoma kinase (ALK) immunoreactivity testing for patients with Stage IIIb or Stage IV non-squamous non-small cell lung cancer and who are negative for mutations of EGFR	Crizotinib	5,791[c]
73342 (available on the MBS since April 2016)	Human epidermal growth factor receptor 2 (HER2) in metastatic adenocarcinoma of the stomach or gastro-oesophageal junction	Trastuzumab	2,118 (stomach) 1,460 (oesophagus)[b]

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, e.g., for patients presenting with metastatic disease.
The 2016 Australian Cancer Incidence and Mortality (ACIM) book. The presented data related to the overall incidence in Australia; NOT related to the number of patients who are eligible for the target therapies.
The 2016 Australian Cancer Incidence and Mortality (ACIM) book. The presented data related to the overall incidence of non-squamous non-small cell lung cancer; NOT related to the number of patients who are eligible for the target therapies. "Lung cancer in Australia: an overview" (AIHW 2011) suggested 53% of all lung cancer to be non-squamous non-small cell subtypes; 5791 = 53% x 10926 (based on the ACIM data).

The assessment report estimates the total number of these pathology test services that could potentially be assisted by the proposed service to be approximately 29,000 per year in the next five years (see Section E for full details). When combined, less than a third of these tests are estimated to be assisted by the proposed service. The base case estimate presented in the current Section E hence suggests the total number of service episodes for the proposed service to be approximately 7,400 per year.

It is important to note the proposed MBS item is not limited to these six test items as more are being considered for listing currently and will continue to be considered in the future by MSAC; the aforementioned utilisation estimate does not capture additional pathology tests that are yet to appear on the MBS listing but are potentially relevant to the assistance of tissue retrieval. Neither does it capture tests currently listed on the MBS, other than the pharmacogenetics tests, to which the service may apply. Furthermore, there are up to 8,000 known rare non-cancer diseases, the majority of which have a genetic origin. While absolute numbers are expected to be relatively low, a small subset of these would benefit from the assistance of tissue retrieval e.g., FISH testing for specific diagnostic translocations.

See Section E for full discussion on the potential usage of the proposed service on the MBS.

A.5 COMPARATOR DETAILS

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

- 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 BSC)
- Retrieval and review by a pathologist without reimbursement (current practice)

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 in to two comparators (No retrieval and patient referred directly for biopsy; No retrieval, no test, and patient remains ineligible for PBS drug).

Given the retrieval and review of archived tissues is already generally accepted practice (PASC Outcomes on Protocol 1331), these proposed comparators should be considered as hypothetical and specifically designed to address the clinical and economic basis for public funding which would justify the provision of the service.

The final comparator (unfunded retrieval and review) was included in the assessment because "PASC considered that the proposed comparator of unfunded retrieval and review of archived tissues would be appropriate in considering the likely impact of public funding on service delivery" (PASC Outcomes on Protocol 1331).

A.6 CLINICAL MANAGEMENT ALGORITHM

Figure 3 outlines the phases of process for diagnostic testing of tumour biopsy and the place of retrieval and review of archival tissue in that process. Taking, for example, a patient who has previously has colorectal cancer, has previously had their primary tumour resected tumour; formalin-fixed paraffin-embedded (FFPE) samples of the tumour tissue have since been archived or banked. The patient has now developed metastatic disease. The treating specialist makes a request to the pathologist that the primary tumour tissue be analysed for RAS mutations to determine whether the patient is eligible for targeted therapy, i.e., cetuximab.

The archived primary tissue may be being stored on-site or at an off-site; it may be at a local archive facility or it may be stored further way, for example if the patient had previously been treated at a different hospital. Once the location of the archival tissue is known, the pathologist at the source laboratory is required to retrieve and review the tissue, select appropriate samples for diagnostic testing and forward the selected samples to the testing facility. The testing may be performed on-site or if on-site testing is not available, then the test will be conducted at an external reference laboratory.

There is a possibility the archival tissue cannot be retrieved or the retrieved tissue is deemed by the

reviewing pathologist as being sub-optimal for testing. There is also the possibility a test will not yield an interpretable result even where the sample was deemed appropriate for testing. In these cases, where no result is obtained, there may be an option for the patient to undergo a repeat biopsy, in which case it may be possible to perform testing on freshly obtained sample tissue. The retrieve and review process by a pathologist is to minimise the of a test failure and optimise the accuracy of the test result.

The overall turnaround time from request to test result will therefore largely depend 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.

Reimbursement for the proposed service requires the retrieve and review process be completed within a maximum of 7 days. According to published guidelines (Aubin et al 2011; CAMP 2015; Lindeman et al 2013; van Krieken et al, 2013), the acceptable turnaround time from the receipt of sample to the reporting of test result for molecular diagnostic testing in cancer is 10 working days. Taken together, this suggests an acceptable overall turnaround for molecular diagnostic testing using archived tissue is 15 working days or 3 weeks. The optimal treatment management of the patient depends on the outcome and timeliness of the test result.

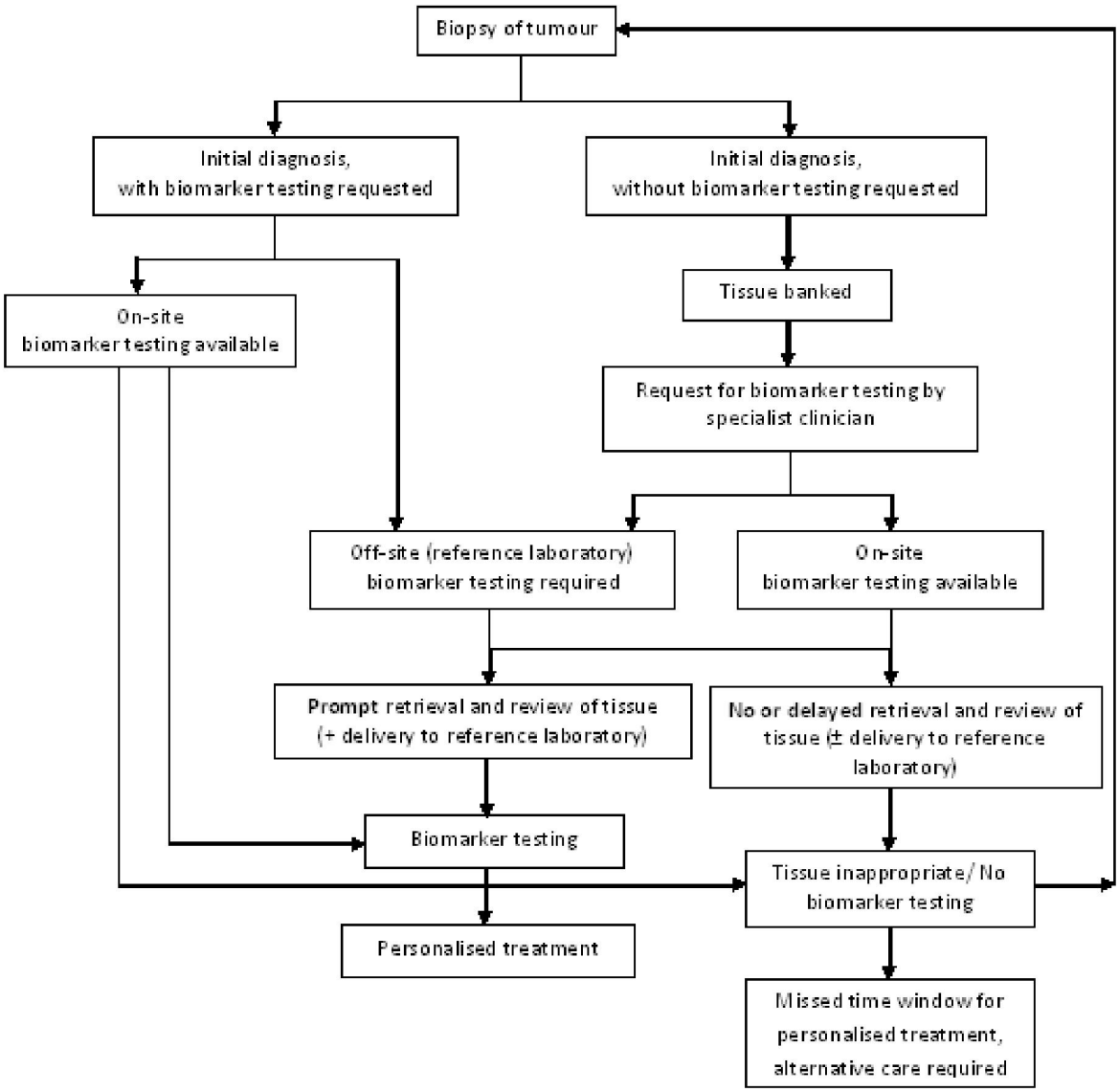

Figure 3 The investigational algorithm and the place of the retrieval and review of tissue samples

A.7 KEY DIFFERENCES IN THE PROPOSED MEDICAL SERVICE AND THE MAIN COMPARATOR

The retrieve and review intervention is already accepted practice prior to the diagnostic testing of archival tissue. The proposed service means the intervention will be reimbursed if it is completed within 7 days. The key differences reimbursement of the proposed medical service will make to patients, physicians and the health care system more generally are summarised in the clinical claim section which follows.

A.8 CLINICAL CLAIM

The overriding claim made in the DAP 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.

Reimbursement for the proposed service requires the retrieve and review process be completed

within a maximum of 7 days. The clinical evaluation in Section B will show turnaround times for archival sample retrieval and review in current practice to be within 7 days in less than 40% of cases (Scott et al. 2014). Assuming at least some laboratories currently taking longer than 7 days will respond to the reimbursement incentive provided by the MBS fee then, the proposed intervention is superior to the main comparator in terms of time taken for an optimal sample to be available for testing. As such, the purpose of the economic model is to quantify the cost and quality of life implications of this improved turnaround time. As such, the form of economic evaluation is cost-utility analysis.

Given the retrieval and review of archival tissues is already generally accepted practice (PASC Outcomes on Protocol 1331), the other comparisons in the assessment are hypothetical and are specifically to address the clinical and economic basis for public funding which would justify the provision of the service. Without direct evidence confirming as such, the proposed intervention can nevertheless be assumed to be superior to each one of these comparators on at least one outcome as follows:

- Compared to retrieval without review:
    - Retrieve and review should reduce the number of tests being conducted on sub-optimal tissue which in turn would reduce costs on futile tests and/or improve diagnostic accuracy
- Compared to no retrieval and patient referred directly for biopsy:
    - Retrieve and review has time, cost and quality of life advantages for the patient
- Compared to no retrieval, no test, and patient remains ineligible for PBS drug:
    - Retrieve and review means those patients who would be eligible for the PBS drug go on to receive the efficacy, effectiveness and QALY gains associated with the PBS treatment

As such, cost-utility analysis is the appropriate form of economic evaluation relative to each of the four comparators.

A.9 SUMMARY OF THE PICO

The guiding framework of a DAP is recommended by MSAC for each assessment. The DAP describes current clinical practice and reflects the likely future practice with the proposed medical service. The modified PICO pre-specified to guide the systematic literature review for evidence, are presented in Box 1.

Box 1 Summary of modified PICO

Selection criteria	Description
Population	Patients who have conditions which may benefit from further testing of previously biopsied archived tissue - [The systematic literature review focuses on of patients who have cancer conditions which may benefit from current MBS funded tests for assessing eligibility for PBS funded co-dependent therapies]
Intervention	MBS funding of the retrieval and review of archived tissues and selection of appropriate samples for further pathological testing
Comparator/s	(i) Retrieval without review (ii) No retrieval and patient referred directly for biopsy (iii) no retrieval, no test, and patient remains ineligible for PBS drug (iv) Unfunded retrieval with review
Outcomes	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; 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?

SECTION B: CLINICAL EVALUATION

B.1 DIRECT EVIDENCE

Archiving pathology samples is a fully disseminated process and current practice is to archive tissue for at least 10 years. Retrieval and review of archival tissues as a service is already generally accepted practice (PASC Outcomes on Protocol 1331).

Expert pathologists have indicated they are not aware of any direct evidence from comparative studies specifically designed to assess the relative benefit of including a retrieve/review intervention prior to undertaking diagnostic testing using archival tissue either with or without funding. Extensive exploratory searching conducted for the preparation of this assessment would concur with this.

Given there is no direct evidence to support either comparison, a linked evidence approach is required to inform the economic modelling and answer research questions outlined in the DAP

B.2 LINKED EVIDENCE APPROACH

B2.1 BASIS FOR LINKED EVIDENCE

As discussed in Section A, the assessment identifies four comparators to the funded retrieval and review intervention by a pathologist prior to undertaking diagnostic testing on archived tissue, namely: 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 BSC) and; retrieval and review by a pathologist without reimbursement (current practice)

Given there is no direct evidence to support any of the above comparisons, a linked evidence approach is required to inform the economic modelling and answer research questions outlined in the DAP

It should be noted archiving and retrieval of pathology samples has been fully disseminated and retrieval and review of archival tissues as a service is already generally accepted practice (PASC Outcomes on Protocol 1331). It would neither be considered good nor standard practice to perform diagnostic testing on archival tissue which had not previously undergone review by a pathologist for its suitability for testing. Therefore, relevant data identified pertaining to molecular diagnostic testing on archival tissue in clinical practice most likely represents the optimal situation. Thus, the first three comparisons can only be hypothetical and the economic evaluations provided in the assessment scenario driven, comparing the hypothetical case to what is current practice.

B2.2 STEPS FOR LINKED ANALYSIS

The linked evidence approach in this assessment is outlined in Figure 4. Given the scenario where archival tissue is retrieved but not reviewed by a pathologist prior to molecular diagnostic testing, the main hypothesis is there would be an increased likelihood of a retrieved archival sample being sub-optimal for testing (e.g., due to insufficient tumour material; poor quality sample etc.) resulting in an increased likelihood of futile testing (i.e., where no result is obtained or a sub-optimal result is

obtained). In the case where there a test result is based on sub-optimal tissue, the diagnostic test performance would be sub-optimal. Where no test result was available, re-biopsy would be required where possible, which would carry an inherent risk of adverse events.

The outcome of the test result determines whether the patient would be eligible for targeted therapy or not (Note: Figure 4 follows the example were a patient found with a KRAS mutation negative tumour, i.e., where the patient's test is negative, the patient is eligible for cetuximab or panitumumab; in tests with other tissues it may be that it is the test positive patients are those eligible for the relevant targeted therapy).

In the case where archival tissue is retrieved but not reviewed by a pathologist, the continued hypothesis is a patient is more likely to obtain a false negative or false positive result and, as a consequence, will go on to receive a sub-optimal therapy or a less cost-effective therapy and, potentially, achieve a poorer survival outcome. In the case where no test result is obtained and a re-biopsy is not possible, then a patient could only receive the standard therapy. Patients would then be assigned the costs and benefits of the treatment received. Patients wrongly assigned the targeted therapy would get the incremental cost and possible detrimental effects of the treatment but not the incremental benefit over standard therapy. Patients correctly assigned the targeted therapy would get the incremental costs and the incremental benefit.

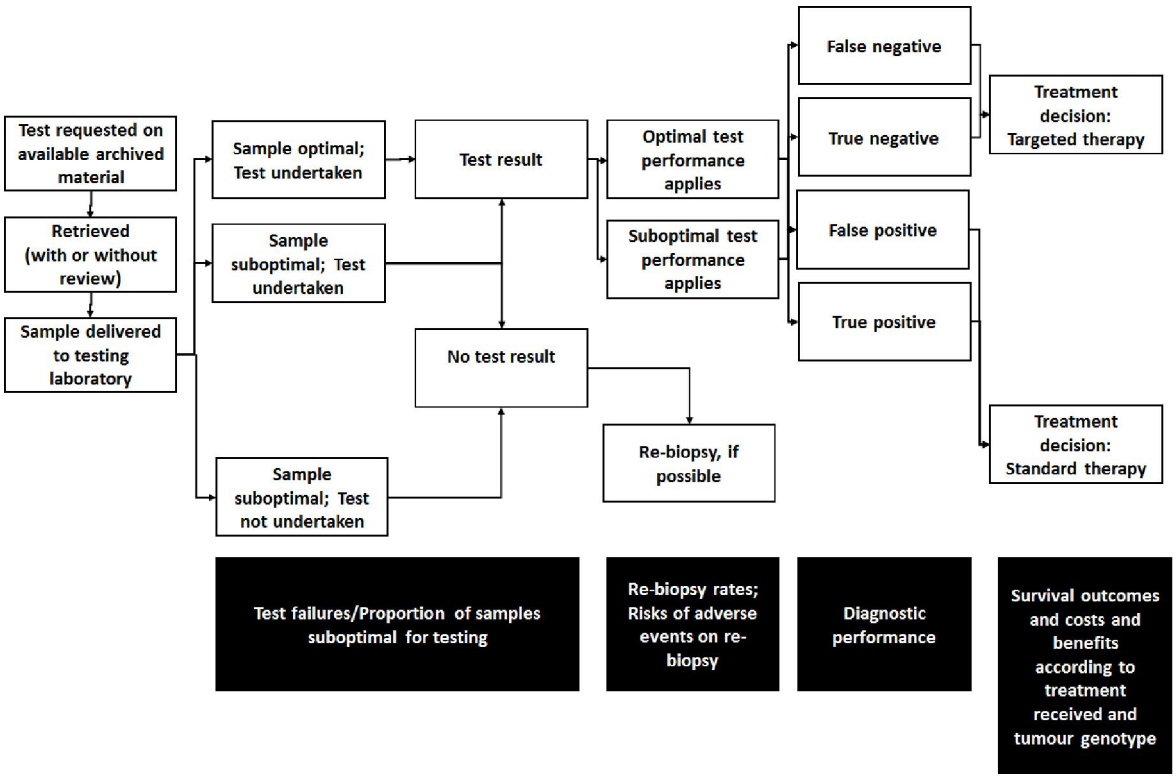

Figure 4 Outline of linked evidence approach

The second hypothesis is the overall turnaround time from when the clinician requests the test request to the when the test result is reported longer when no pre-analytic review by a pathologist is included in the process (Figure 5) and that this potentially results in delayed treatment or the

administration of a sub-optimal therapy or the possibility a patient develops a disease progression prior to a treatment decision being made.

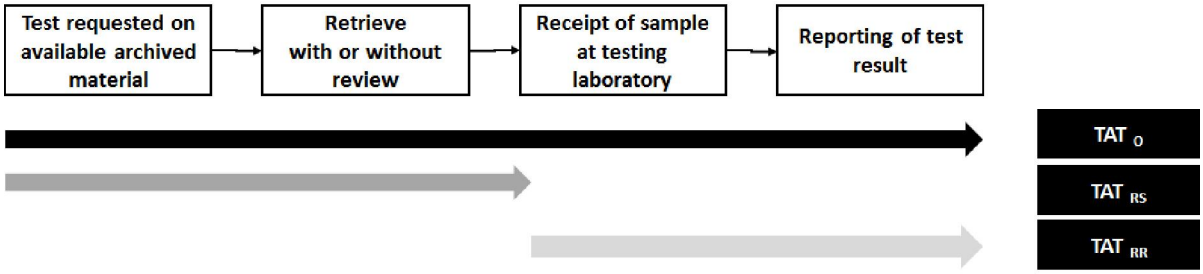

Figure 5 Turnaround time

The objective is therefore to collect and link evidence in the context of diagnostic testing using archival tissue samples in relation to test failures, 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 electronic literature searches presented in Section B3 of this assessment were conducted in order to identify evidence regarding the process of molecular diagnostic testing in clinical practice with a focus on test success or failure and test turnaround times. The systematic literature review focused on of patients who have cancer conditions which may benefit from current MBS funded tests for assessing eligibility for PBS funded co-dependent therapies.

Further linked evidence regarding diagnostic performance, survival outcomes and incremental costs and benefits of receiving targeted therapy compared to standard therapy according to tumour genotype will rely on information available in relevant MSAC and PBAC PSDs relating to molecular diagnostic tests listed on the MBS and associated co-dependent therapies listed on the PBS. The use of the MSAC and PBAC PSDs as a primary information source is considered justified on the basis the data supporting the diagnostic performance and clinical validity of each of the tests and their respective impacts on clinical management have already been reviewed and accepted by the MSAC and PBAC. The information derived from the PSDs will be documented within Section C.4.

B.3 MOLECULAR DIAGNOSTIC TESTING ON ARCHIVAL TISSUE IN CLINICAL PRACTICE: TECHNICAL EVIDENCE ON PROCESS

B3.1 LITERATURE SOURCES AND SEARCH STRATEGIES

Two electronic database searches of the published literature (MEDLINE+ EMBASE [www.embase.com]) were undertaken.

Search 1: To identify studies where diagnostic testing has been undertaken in clinical practice using archival tissue

The first search was designed to identify observation studies (e.g. audits; chart-reviews; case series etc.,) where diagnostic testing had been undertaken in the clinical practice setting i.e., with a view to patient management using, and where testing had been carried out using archival tumour tissue.

The search was focused on the five molecular diagnostic tests currently listed as items on the MBS to select patients for targeted cancer therapies available on the PBS (i.e., the diagnostic tests for BRAF V600 gene mutations in melanoma, KRAS mutations in metastatic colorectal cancer, epidermal growth factor receptor (EGRF) mutations in non-squamous non-small cell lung cancer (NSCLC), anaplastic lymphoma kinase (ALK) rearrangement in non-squamous non-small cell lung cancer using FISH, and human growth factor receptor 2 (HER2) gene amplification in breast cancer or in metastatic adenocarcinoma of the stomach or gastro-oesophageal junction using ISH. The reason being these tests are the ones frequently requested on archive tissue in Australian clinical practice and therefore most likely to be the tests invoking the proposed service.

Search 2: To identify studies monitoring the turnaround time of diagnostic testing has in clinical practice

The second search was designed to identify observation studies (e.g. audits; chart-reviews; case series etc.,) where diagnostic testing had been undertaken in the clinical practice setting i.e., with a view to patient management using and where the turnaround time of testing had been assessed.

Again, the search focused on the five molecular diagnostic tests currently listed as items on the MBS to select patients for targeted cancer therapies available on the PBS. However, the search was not confined to testing which had been carried out using archival tumour tissue.

A detailed description of the search strategies and the results of the searches are presented in Appendix A. The searches were conducted on 5 July 2016.

Full citation details and abstracts were downloaded and scrutinised for all records identified in the search.

For inclusion, the study had to be:

- a study of diagnostic testing undertaken as a requested pathology service, or as part of a screening program, with a view of treatment management of the patient
- where diagnostic testing included one of the tests of focus in the same indication for which the test is listed on the MBS
- where reported outcomes included test turnaround time and /or test failure rate

Citations identified in each of the searches were evaluated using the following predefined exclusion criteria:

- Citation does not pertain to a study of diagnostic testing undertaken as a requested pathology service, or as part of a screening program, with a view of treatment management of the patient

- Citation does not pertain to one of the tests of focus in the same indication for which the test is listed on the MBS
- Citation does not report on any of the following outcomes:
    - The test turnaround time (TAT_O, TAT_{RS}, TAT_{RR}) where:
        - TAT_O represents the overall turnaround time from the ordering of the test by the clinician to the reporting of the test result back to the clinician,
        - TAT_{RS} represents the time from the ordering of the test to the receipt of tissue sample at the testing facility, and
        - TAT_{RR} represents the time from the receipt of the sample at the testing facility to the reporting of test result back to the clinician.
    - Test failure rate, either due to
        - No test, e.g., where a sample is lost or sub-optimal for testing
        - Test/No result, e.g., where the sample is analysed/tested but the test yields no result

If a citation could not be excluded on the basis of the information in the title or abstract, the full paper was retrieved and reviewed.

Initially, it had been intended to exclude citations if they did not pertain to molecular diagnostic testing conducted in archival or banked tissue. However, during the screening process, it was frequently difficult to ascertain whether or not testing had been conducted on banked or archival tissue. Consequently, no citations were excluded on this basis. Instead, the data extraction noted whether the use of archival tissue had been specified within the source publication.

Citations were excluded also if they were guidelines on molecular diagnostic testing; position pieces or reviews on molecular diagnostic tests; qualitative discussions regarding pre-analytical and analytical determinants of molecular diagnostic test performance. However, the reference lists provided in these articles were searched for citations of potential relevance.

Additional citations providing information of potential relevance

During the abstract screening, citations excluded on the basis of the listed criteria were additionally flagged for further review if they fell into one of the following three categories and contained potentially useful information with regard to sample suitability for testing or TAT:

- Citation pertains to genomic panel testing undertaken as a requested pathology service, or as part of a screening program, with a view of treatment management of the patient
- Citation pertains to tumour characterisation (using one of the 5 tests of focus in the same indication for which the test is listed on the MBS) undertaken purely for tumour research purposes or test method development or test performance

- Citation pertains to tumour characterisation by genomic panel testing undertaken purely for tumour research purposes or test method development or test performance

B3.2 RESULTS OF LITERATURE SEARCH

The results of the electronic database searches (Search 1 and Search 2) are summarised in Table 12and in the PRISMA Flow diagram provided in Figure 6 and Figure 7.

For Search 1, a total of 938 unique citations were identified, including 2 citations identified through hand searching. Of these, 931 were excluded in the first pass screen based on the content of the titles and abstracts. The majority of the records identified in the search were conference abstracts. With the exclusion of multiple citation of the same study, Search 1 identified a total of 6 unique studies meeting the search inclusion criteria. An additional 22 excluded studies (23 excluded citations) were flagged as having potentially relevant information.

For Search 2, a total of 170 unique citations were identified, including 2 citations identified through hand searching. Of these, 140 were excluded in the first pass screen based on the content of the titles and abstracts. The majority of the records identified in the search were conference abstracts. A further 3 citations were excluded following review of the full journal article. With the exclusion of multiple citation of the same study, Search 2 identified a total of 24 unique studies meeting the search inclusion criteria. An additional 4 excluded studies were flagged as having potentially relevant information, one of which was already flagged from Search 1.

Excluding duplicated citations across searches, Search 1 and Search2 combined identified a total of 27 unique studies meeting the search inclusion criteria. A total additional 25 excluded studies flagged as having potentially relevant information.

Table 12 Summary of identification of relevant evidence from the published literature

	MEDLINE + EMBASE
Search 1 – *Search date: 5 July 2016*	
Number of citations identified through database searching	950
Additional citations identified by hand search	2
Number of exact duplicate citations	14
Number of unique citations retrieved by search	938
Number of citations excluded after title/abstract review: Testing not a requested service routine screening Test not one of focus in correct indication Does not report outcomes of interest Total	 574 358 0 932
Number of citations excluded after full text review Testing not a requested service routine screening Testing not one of focus in correct indication Does not report outcomes of interest	 0 0 0
Number of included citations	6
Number of excluded multiple citations of same study	2
Number of unique included studies	4
An additional 22 excluded studies were flagged as having potentially relevant information	
Search 2 – *Search date: 5 July 2016*	
Number of citations identified through database searching	170
Additional citations identified by hand search	2
Number of exact duplicate citations	2
Number of unique citations retrieved by search:	170
Number of citations excluded after title/abstract review: Testing not a requested service routine screening Test not one of focus in correct indication Does not report outcomes of interest Total	 137 0 3 140
Number of citations excluded after full text review: Testing not a requested service routine screening Testing not one of focus in correct indication Does not report outcomes of interest Total	 2 1 0 3
Number of included citations	27
Number of excluded multiple citations of same study	3
Number of unique included studies	24
An additional 3 excluded studies were flagged as having potentially relevant information	
Search 1 and Search 2 combined	
Total number of studies identified in Search 1	4
Total number of studies identified in Search 2	24
Number of duplicated included studies	1
Number of unique included studies	27
An additional 25 excluded studies were flagged as having potentially relevant information (one citation was duplicated across searches)	

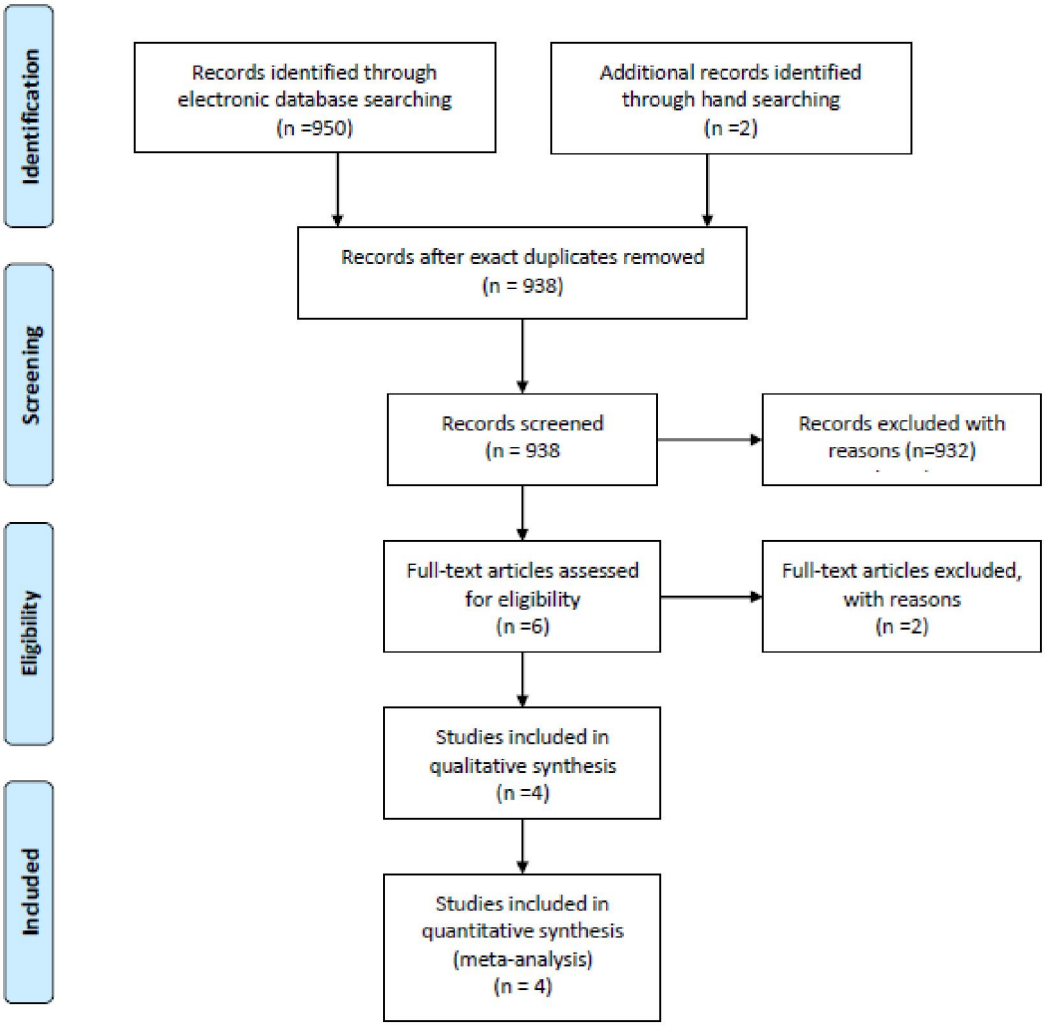

Figure 6 PRISMA Flow diagram – Search 1

See Table 12 for reasons for exclusion

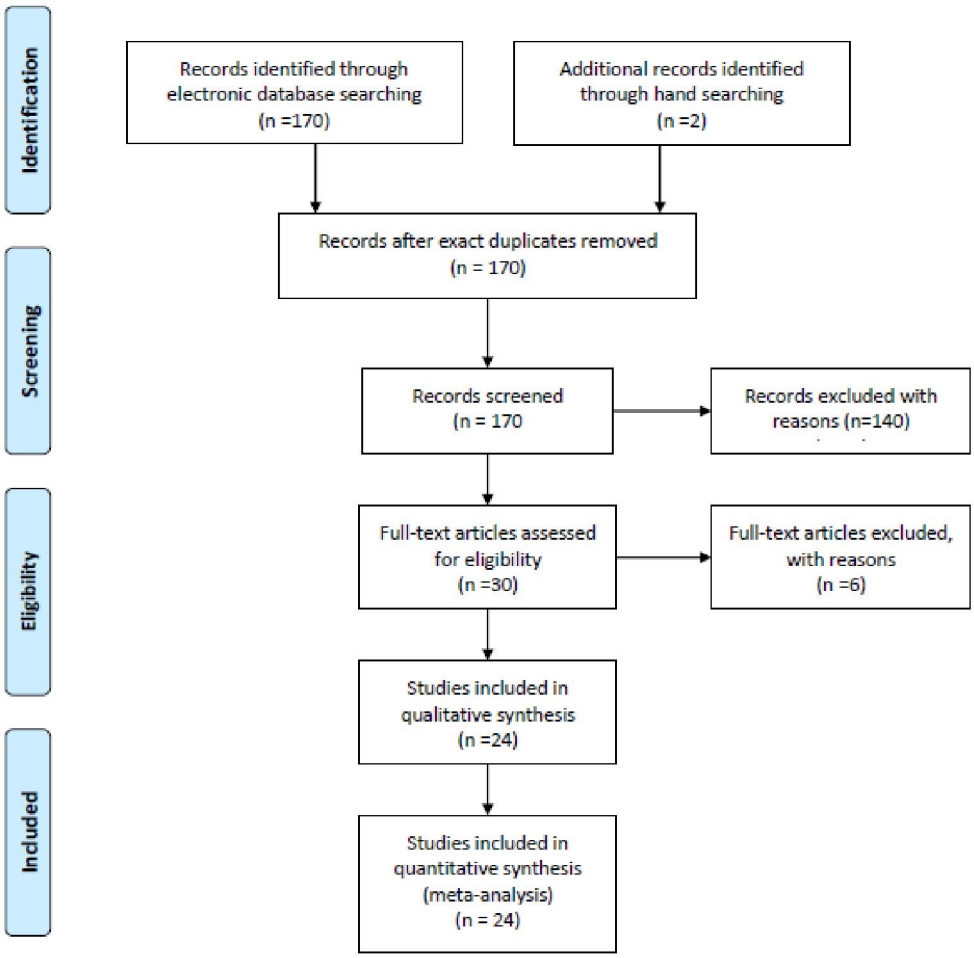

Figure 7 PRISMA Flow diagram – Search 2

See Table 12 for reasons for exclusion

CONCLUSION

The evidence data base for this assessment comprises 27 unique studies describing diagnostic testing undertaken either as a requested service or as routine in clinical practice for the management of patients and where the testing involved one or more of the five molecular diagnostic tests currently listed as items on the MBS to select patients for targeted cancer therapies available on the PBS. An additional 24 excluded studies where were flagged as also having potentially relevant information.

B3.3 RISK OF BIAS ASSESSMENT

The evidence database contains a disparate collection of retrospective, retro-prospective and cross-sectional observational studies from different locations and settings with differing overarching objectives. Much of the published information is limited to conference abstracts. On this basis, no formal risk of bias assessment is presented.

B3.4 CHARACTERISTICS OF THE EVIDENCE BASE

The main characteristics of the twenty-seven included studies identified in the two electronic database literature searches combined are summarised in Table 13. Note, the majority of the reports (15/27) of the studies are confined to conference abstracts, consequently the information contained within these is limited in terms of detail. The studies included multi-national, national, regional and single institution and retrospective, retro-prospective and cross-sectional studies. The publication dates ranged from 2009 to 2016. The testing periods reported upon ranged from 2008 to 2015. Studies were from Australia (1), Belgium (1) Brazil (1), Canada (3), France (6), Spain (2) UK (5), and the US (6) and two studies were multi-national (Europe; Asia/Europe/Latin America).

Ten studies reported specifically on KRAS or RAS testing for the management of patients with mCRC. Ten studies reported on EGFR mutation testing in the management of patients with NSCLC. Of these ten, two also reported on testing for ALK rearrangements (one specifying the use of FISH). Six studies reported on HER2 testing using ISH in the management of patients with breast cancer (4 studies) or gastro-oesophageal cancer (1 study). One study reported on biomarker testing, including testing for KRAS, BRAF and EGFR mutations in in various solid tumours including CRC and lung. No studies were of BRAF mutation analysis in the management of patients with melanoma.

Where diagnostic testing involved DNA mutation analysis, a variety of methodologies were employed and testing mainly involved the use of FFPE tissue. However, the source information did not always specify whether the tissue was necessarily archival FFPE tissue. Only in nine studies (Bibeau 2010; Bibeau 2012; Chretien 2013; Lievre 2013; Scott 2014; Tsao 2011; Raetskaya-Solntseva 2012; Lim 2015; Lim 2013) could it be ascertained testing was mostly or exclusively on archival tissue; 3 of these studies (Bibeau 2010; Chretien 2013; Tsao 2011) additionally specified the archival tissues had been reviewed by a pathologist prior to testing. However, if adherence to standard good practice can be assumed throughout, the all archival tissues would have been reviewed prior to testing. With the exception of two studies (Janssens 2014; Goom 2012) which appear to have undertaken tests exclusively on freshly obtained tissues, the use of archival tissue cannot be ruled out. in the remaining studies.

Twenty-five studies reported on the test turnaround time as TAT_O, TAT_{RS} or TAT_{RR}; twelve studies reported on test failure rate, with or without reasons, one study reported on repeat biopsy rate.

Table 13 Summary of observation studies of single molecular diagnostic testing undertaken as a requested or routine pathology service with a view of treatment management

Lead author/Year	Citation type	Country	Diagnostic test and test population	Context of study	Patients/Cases/ Tests/requests	Data collection	Test method(s)	Use of archive tissues	Outcomes reported potentially relevant to this submission
Bibeau 2010[a,b,c]	Conference abstract	France	KRAS mutation testing in mCRC	A retrospective one year observation study of KRAS mutation testing in clinical practice	575 samples	Tests between May 2008-May 2009	Not reported	Reviewed archival FFPE tissues;	Test failures
Ciardiello 2011	Full journal article	Europe (6 countries); Latin America (5 countries); Asia (2 countries)	KRAS mutation testing in mCRC	Yearly cross-sectional survey (quantitative questionnaire of physicians including review of the records of 4 *a priori* designated mCRC patients (last seen, last seen in first, second and third line settings)	2008: 113 tests 2009: 1775 tests 2010: 2619 tests	Survey years: 2008-2010	Not reported	Not specified whether testing was on newly acquired, archive tissue or either	TAT_O Test failures
Bibeau 2012	Full journal article	France	KRAS mutation testing in mCRC	Retro-prospective study of access to KRAS mutation testing of patients with mCRC across 66 institutions	329 patients	Testing undertaken Oct 2008-Oct 2009	Mostly RT-PCR; sequencing; pyrosequencing	Testing was on primary tissue and surgical samples	TAT_O Test failures

Lapeyrere 2012	Full journal article	France	KRAS mutation testing in CRC	Retrospective study of KRAS analysis management in KRAS mutation testing laboratories (Acquitaine);	302 analyses	Jan 2009 - March 2009	Not specified	FFPE archival tissue used	TAT_O
Chretien 2013	Full journal article	France	KRAS mutation testing in mCRC	Review of analysis of tissues by single testing centre for routine testing	674 samples	Collected for assessment between Jan 2008 – Dec 2009	High resolution melting; PCR-RFLP; allelic discrimination PCR	Reviewed FFPE tissues; mainly primary tissue	Test failures TATo
Lievre 2013; Artu 2012; Ducreux 2011 Flash-KRAS study	Full journal article; Conference abstract	France	KRAS mutation testing in mCRC	Observational retrospective study of initial management of mCRC in 160 hospital centres	538 cases/ 433 test requests	Tests requested during a 2-week period in March 2011-Apr 2011	Mostly sequencing; pyrosequencing; SNaPshot; allelic discrimination; high resolution melting	Testing was mainly (86.1%) on the primary tumour tissue; 14.5% of testing was prior to the diagnosis of first metastases	TAT_O TAT_{RS} TAT_{RR} Test failure Biomarker directed treatment management
Scott 2014	Full journal article	Australia	KRAS mutation testing in mCRC	Audit of routine KRAS testing in by 9 major NATA accredited molecular pathology service providers	3688 cases (TAT available for 2531 cases [4 of the 9 testing facilities])	Tests requested between Sept 2011-Oct 2013	Various: Sanger direct (3 sites); pyrosequencing (2 sites); single nucleotide base extension using Sequenom Massarray (2 sites); Sanger sequencing, then SNaPshot (1site); HRM then Sanger	~25% from biopsy; 75% surgically resected tissue from FFPE blocks of the primary tissue (i.e., 75% archive tissue	$TAT_{O;}$ $TAT_{RS;}$ $TAT_{RR;}$ Proportion of cases with a given $TAT_{O;}$

							sequencing (1 site)		
Boleij 2015	Conference abstract	24 countries in Europe	RAS- mutation testing in mCRC	Survey of 96 pathology laboratories undertaking RAS testing in clinical practice in Europe; information provided on approximately 20-30 of the most recent tested mCRC patients	3,972 patients	Survey took place Oct 2014-Dec 2014	Various	Included FFPE tissue; not specified whether testing was on newly acquired, archive tissue or either	TAT_O
Lievre 2015 Flash-RAS study	Conference abstract	France	KRAS mutation testing in mCRC	Observational multi-centre retrospective study of RAS testing in mCRC in clinical practice; 104 centres	375 patients	Mar 2014-June 2014	Not specified	Not specified whether testing was on newly acquired, archive tissue or either	TAT_O
Lowe 2016	Conference abstract	US	KRAS, NRAS and BRAF mutation testing in mCRC	Retrospective review of testing in community cancer centres (OSCER database)	1550 patients	Diagnosed between Jan 2011-Aug 2015	Not specified	Not specified whether testing was on newly acquired, archive tissue or either	TAT_O
Gracia 2011	Conference abstract	Spain	EGFR mutation testing in non-squamous NSCLC	Prospective epidemiological study to gain insight into variables that affect the	1009 patients with available sample	6-month study; date not reported	Various	Biopsy and cytological sample; not specified whether testing was on	TAT_O Test failures

				feasibility and implementation of EGFR mutation testing in routine clinical practice; 39 Spanish centres using two central testing centres and 7 on-site testing facilities				newly acquired, archive tissue or either	
Tao 2011	Conference abstract	Canada	EGFR mutation testing in advanced non-squamous NSCLC	Result from pilot routine testing network NSCLC involving 5 testing laboratories	1869 requests	March 2010 – Nov 2010	Not specified	Reviewed, archive FFPE includes tissue and cytology samples	Test failures TAT_{RS} TAT_{RR}
Leary 2012	Full journal article	UK	EGFR mutation testing in advanced non-squamous NSCLC	Study of the feasibility of prospective EGFR testing in routine clinical practice; single testing centre	Year 1: 152 samples (144 cases) Year 2: 755 cases	Screening period: Jan 2009 - Jan 2010; Jan 2010 - Jan 2011	Year 1: TheraScreen EGFR29 ARMS mutation kit; Year 2: Combination of ARMS; fragment analysis; direct sequencing	Blocks or slides; not specified whether testing was on newly acquired, archive tissue or either; some samples were from external sources	Test failures TAT_{O} TAT_{RS}
Raetskaya-Solntseva 2012	Conference abstract	US	EGFR and ALK mutation testing in NSCLC	Retrospective observation study to determine the utility of a reflex testing policy for the mutations:	63 prior to policy; 123 post	6 months before and 6 months after introduction of reflex policy	Not specified	FFPE archival tissue used	TAT_{O}

Baldotto 2013	Conference abstract	Brazil	EGFR mutation testing in NSCLC	Retrospective study of EGFR testing in one centre after introduction of reflex testing; single centre	189 of 336 screened	May 2011-May 2013	PCR; Sanger sequencing	Cytological samples and tumour tissue; unclear how much was archival	TAT_O
Cankovic 2013[a, b]	Conference abstract	US	EGFR mutation and ALK translocation testing in NSCLC	Four phase exercise to streamline process from pre-analytic to reporting phase of molecular testing for EGFR/ALK mutations	111 cases tested	Mar 2011-Sept 2012	Not reported	Not reported	TAT_O
Ellis 2013	Full journal article	Canada	EGFR mutation testing in advanced non-squamous NSCLC	Prospective validation/QC exercise for implementation of routine EGFR testing strategy in NSCLC involving 5 testing laboratories	2104 test requests	Tests requested between Mar 2010-Dec 2010	RT-PCR	Blocks or slides; not specified whether testing was on newly acquired, archive tissue or either	Test failures TAT_O RAT_{RS} TAT_{RR}
Arriola 2014	Conference abstract	Spain	EGFR mutation in advanced NSCLC	Retrospective observation study of the management patterns of advanced EGFR mutated NSCLC pts in	181 evaluable patients	Patients diagnosed Apr 2010-Dec 2011	RT-PCR	Mainly biopsy material	TAT_O

				Spain; 8 centres; Testing mainly done in external laboratories					
Janssens 2014	Full journal article	Belgium	EGFR mutation testing in NSCLC	Data collection from testing of patients in clinical care by two central testing facilities	107 samples tested	Not specified	Not specified	Tissues collected prospectively; not archival tissue	Test failures TAT_O
Lim 2015	Full journal article	Canada	EGFR mutation and ALK rearrangement testing in advanced NSCLC	Retrospective chart review of EGFR mutation and ALK rearrangement testing of a random sample of 25% of patients with advanced NSCLC in a single centre	300 cases of which focus was on 258 cases of non-squamous NSCLC of which 126 underwent diagnostic testing at the institution of which 99 testing requests were initiated by the oncologist at the initial consultation (27 cases already had test results available)	Referrals from April 2010 – March 2013	EGRM mutation testing by PCR fragment analysis; ALK testing by IHC confirmed by FISH	Included testing of archival and new tissue; 27/126 (21%) of results available at first consultation; 99/126 978.65) not available at initial consultation	Test failures Cases where repeat biopsies undertaken Cases where rebiopsy provided adequate tissue for analysis TAT_O Biomarker directed treatment management
Fergusson 2009	Conference abstract	UK	HER2 testing in breast cancer	Retrospective observation study of length of time of testing process; single centre (tests undertaken centrally)	49 cases	Apr 2006-Apr 2007	Not specified	Not specified whether testing was on newly acquired, archive tissue or either	TAT_O

Goom 2012	Conference abstract	UK	HER2 testing in breast cancer	Internal audit of testing timelines in a single testing facility serving 10 hospitals	814 test requests	Not specified	Not specified	Biopsy material (not archival material)	TAT_O
Lim 2013	Full journal article	US	HER2 testing in breast cancer	Review of previously testing Single centre	101 selected cases	Samples identified in archive between May 2010 – Nov 2011	FISH	Archival FFPE tissue	TAT_O
Shabaan 2014	Full journal article	UK	HER2 testing in breast cancer	Process mapping from three recognised laboratories	Not reported	Not reported	ICH and FISH	Core biopsy and/or resected material; not specified whether testing was on newly acquired, archive tissue or either	TAT
Steinmetz 2014	Conference abstract	US	HER2 testing tumour type not specified	Multiple phase exercise to streamline process from pre-analytic to reporting; single test lab study	Not applicable	Not applicable	FISH	FFPE tissue; Not specified whether testing was on newly acquired, archive tissue or either	TAT_O
Butt 2013	Conference abstract	UK	HER2 testing in oesophagogastri tumours	Review of previous testing over 2.5 years; single referral laboratory	844 test referrals	Not specified	F/DDISH	FFPE tissue; Not specified whether testing was on newly acquired,	Adequacy of sample TAT_{RR}

								archive tissue or either	
Reddy 2010	Conference abstract	US	Biomarker testing in tumour tissues	Review of routine biomarker testing (various including KRAS BRAF and EGRF) in various cancers including CRC, lung and other in a community setting	104 consecutive patients	Review undertaken between Aug 2008-Dec 2009	RT-PCR	FFPE tissue; Not specified whether testing was on newly acquired, archive tissue or either	TAT_O TAT_{RS} Test failures

Abbreviations: ALK, anaplastic lymphoma kinase; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; FISH, fluorescence in situ hybridisation; FFPE, formalin-fixed paraffin-embedded; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; KRAS, Kirsten rat sarcoma; mCRC, metastatic colorectal cancer; NSCLC, non-small cell lung cancer;
TATo = Overall turnaround time from ordering of test to reporting of test result; includes time of retrieval and review of archival tissue where applicable;
TAT_{RS} = Time from ordering of test to receipt of sample at test facility, includes time of retrieval and review of archival tissue where applicable
TAT_{RR}= Time from receipt of sample at test facility to reporting of test result

The main characteristics of the 24 additional excluded studies flagged as having potentially relevant information are summarised according to the categorisation of the study. Of the 8 studies of genomic panel testing as a requested service or part of routine screening (Table 14); five studies reported on the test turnaround time; five reported on test failure rate; two studies reported on repeat biopsy rates associated adverse event rates (one of which also reported on biopsy failure rate). All twelve studies of single biomarker testing undertaken as part of method development, assessment of test performance or tumour characterisation for research purposes (Table 15) reported on test failure rate. Of the five studies of genomic panel testing undertaken as part of method development assessment of test performance or tumour characterisation for research purposes (Table 16), four studies reported on the test turnaround time and three reported on test failure rate.

Table 14 Summary of studies of evaluating gene panel testing of tumours, with a view of treatment management or placing patients into early phase clinical trials

Lead author/Year	Citation type	Country	Diagnostic test	Context/Study type	Patients/Cases /Tests/requests	Date	Test method(s)	Use of archive tissue	Outcomes reported potentially relevant to this submission
Tran 2011	Conference abstract	Canada	Multi-platform molecular profiling in patients with advanced solid tumours	Feasibility of prospective molecular profiling of tumours; 5 centre study	15 enrolled patients (14 tested) (preliminary report)	Not reported	Targeted mutation analysis (Sequenom Mass Array); Targeted exome sequencing; confirmed by Sanger sequencing	FFPE and snap frozen; new and archive tissue	Test failures TAT_O TAT_{RR} Biopsy failure rate Biopsy adverse events
Bedard 2013	Conference abstract	Canada	Targeted gene testing panel of various advanced solid cancers	Trial screening program to match patients with target therapies; Single institution	485 patients	Patients enrolled between Mar 2012 – Jan 2013	Next generation sequencing	Exclusively testing in archival FFPE tissue	Test failures
Takahashi 2013	Conference abstract	Japan	Pan-cancer gene panel screening for advanced solid tumours	Feasibility study of multiplex screening; single centre	105 patients	Patients enrolled between Jul 2012-Feb 2013	Next generation sequencing	FFPE tissues, mainly archive	Test failures Biopsy adverse events Re-biopsy rate
Yardley 2013	Conference abstract	US	Cancer gene panel screening in metastatic breast cancer	Community based molecular profiling initiative for identifying candidates for targeted therapies	101 samples	Samples profiled between Oct 2012 – May 2013	Next generation sequencing	Exclusively testing in archival FFPE tissue	Test failures
Morris 2014	Conference abstract	US	Cancer gene panel screening	Feasibility study of large scale screening in	400 cases	Patients enrolled between Aug	IHC, gene sequencing,	Not specified whether testing was on newly	Test failures TAT_{RS}

Lead author/Year	Citation type	Country	Diagnostic test	Context/Study type	Patients/Cases /Tests/requests	Date	Test method(s)	Use of archive tissue	Outcomes reported potentially relevant to this submission
			in mCRC,	mCRC to identify eligibility for phase I and II clinical ATTACC companion – experience from one centre		2010-Aug 2013	CIMP assay	acquired, archive tissue or either	TAT_{RR}
Schwaederle 2014	Full journal article	US	Genomic testing panel of various solid tumours of treatment experienced patients	Experience of a molecular tumour board at a single centre: review of consenting patients	34 cases	Enrolled since Dec 2012	Next generation sequencing; IHC, CISH, FISH, PCR; Full exome sequencing	Included testing of archive or new tissue sample; 20/34 samples were from primary tissue	TAT_O
Smith 2014	Conference abstract and poster presentation	US	Genomic biomarker profiling in mCRC,	Pilot study of the feasibility of routine genomic profiling in mCRC patients	50 cases	Enrolled between Jul 2013 – Oct 2013	Next generation sequencing	Exclusively testing in archival FFPE tissue slides or blocks	TAT_{RS}
Toulmonde 2014	Conference abstracts	France	Genomic testing panel of various solid tumours	Genomic screening for eligibility for early phase clinical trials; Experience of a molecular tumour board at a single centre	542 cases	Jan 2014-June 2015	Next generation sequencing; comparative genomic hybridsation	Included testing of archive or new tissue sample	TAT_O

Abbreviations: ALK, anaplastic lymphoma kinase; CISH, chromogenic in situ hybridisation; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; FISH, fluorescence in situ hybridisation; FFPE, formalin-fixed paraffin-embedded; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; KRAS, Kirsten rat sarcoma; mCRC, metastatic colorectal cancer; NSCLC, non-small cell lung cancer; PCR, polymerase chain reaction RT, real time

TATo = Overall turnaround time from ordering of test to reporting of test result; includes time of retrieval and review of archival tissue where applicable; TAT_{RS} = Time from ordering of test to receipt of sample at test facility, includes time of retrieval and review of archival tissue where applicable; TAT_{RR}= Time from receipt of sample at test facility to reporting of test result

Table 15 Summary of single biomarker testing undertaken as part of diagnostic test method development, assessment of test performance or tumour characterisation for research purposes

Lead author/Year	Citation type	Country	Diagnostic test	Context/Study type	Patients/Cases/Tests/requests	Date	Test method(s)	Tissue source	Outcomes reported potentially relevant to this submission
Van Cutsem 2008	Conference abstract	Multi-national	KRAS mutation testing in mCRC	Retrospective study of KRAS mutation status of patients in the CRYSTAL trial of cetuximab	578 of 1198 randomised patients	Not reported	Mutation specific quantitative PCR	Archive tissue used	Test failures i
Carotenuto 2010	Full journal article	Italy	KRAS mutation testing in CRC	Test method development for use in clinical practice	540 samples	Not specified	RT-PCR; sequencing	FFPE tissues; Not specified whether testing was on newly acquired, archive tissue or either	Test failures
Dantes 2010	Conference abstract	Germany	KRAS mutation testing in mCRC	Retrospective testing of patients with CRC; single centre study	274 Cases	Resections between 1993 - 2003	Tissue microarray analysis; mutation directed analysis	Archive FFPE tissue from primary tumour	Test failures
Abdulkareem 2012a and b	Conference abstract/ Full journal article	UK	KRAS and BRAF mutation analysis in Nigerian CRC	Retrospective testing of patients with CRC; single centre study	200 cases	Not reported	Pyrosequencing	Archive FFPE tumour tissue	Test failures
Spigel 2010	Conference abstract	US	EGFR and KRAS mutation analysis in NSCLC	Retrospective testing of patients included in a clinical trial	128 patients	Not reported	Not reported	Archive tissue	Test failures
Morgan 2011	Conference abstract	Multi-national	EGFR and KRAS mutation analysis in	Re-evaluation of archival tissue previously	146 samples	Not reported	DxS ARMS Kit	Archival biopsy	Test failures

Lead author/Year	Citation type	Country	Diagnostic test	Context/Study type	Patients/Cases/Tests/requests	Date	Test method(s)	Tissue source	Outcomes reported potentially relevant to this submission
			NSCLC	considered inadequate for mutation analysis				samples	
Dingemans 2011	Conference abstract	Netherlands	EGFR and KRAS mutation analysis in NSCLC	Retrospective testing of patients with chemo-naive advanced NSCLC treated with a platinum doublet	188 cases where tissue avilable	Not reported	High resolution melting following sequencing	Archival FFPE tissue	Test failures
Halblass 2011	Conference abstract	Germany	EGFR, ALK, BRAF and KRAS mutation analysis in NSCLC	Part prospective, part retrospective testing of patients	88 patients	Not reported	Various	Reviewed archival FFPE tissue	Test failures
Subramonia 2012	Conference abstract	US	EGFR mutation testing in NSCLC	Retrospective chart review of patients with NSCLC; single centre;	64 cases	Diagnosed during 2010; reviewed 2011	Not applicable	Archival tissue	On review. adequacy of biopsy samples for potential testing
Wu 2014	Conference abstract	US	EGFR and KRAS mutation testing in NSCLC	Method development using previously tested tissue; Single centre	15 samples	Not reported	Cell enriched transfer; PCR	Reviewed archive FFPE tumour tissue	Test failures
Madrid 2004	Full journal article	Philippines	HER2-/neu testing in breast cancer	Evaluation of CISH assay; single centre study	160 randomly selected HER2+ cases	Testing between 2000-2001	CISH	Archival FFPE primary breast tumour tissue	Test failures
Penault-Llorca 2008	Full journal article	France	HER2 testing in breast cancer	Retrospective testing of tissues	710 Cases	Cases between 1982-2004	Not reported	Archival FFPE primary breast	Availability of usable sample

Lead author/Year	Citation type	Country	Diagnostic test	Context/Study type	Patients/Cases/Tests/requests	Date	Test method(s)	Tissue source	Outcomes reported potentially relevant to this submission
				from before and after chemo therapy; multi-centre study				tumour tissue	

Abbrevaitions: ALK, anaplastic lymphoma kinase; CISH, chromogenic in situ hybridisation; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; FISH, fluorescence in situ hybridisation; FFPE, formalin-fixed paraffin-embedded; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; KRAS, Kirsten rat sarcoma; mCRC, metastatic colorectal cancer; NSCLC, non-small cell lung cancer; PCR, polymerase chain reaction RT, real time

TATo = Overall turnaround time from ordering of test to reporting of test result; includes time of retrieval and review of archival tissue where applicable; TAT_{RS} = Time from ordering of test to receipt of sample at test facility, includes time of retrieval and review of archival tissue where applicable; TAT_{RR}= Time from receipt of sample at test facility to reporting of test result

Table 16 Summary of studies of genomic panel testing undertaken as part of method development, assessment of test performance or tumour characterisation for research purposes

Lead author/Year	Citation type	Country	Diagnostic test	Context/Study type	Patients/Cases /Tests/requests	Date	Test method(s)	Use of archive tissue	Outcomes reported potentially relevant to this submission
Peeters 2010	Conference abstract	Mulit-national	Multi-cancer gene testing for profiling mCRC	Re-examination of clinical trial participants previously tested for KRAS mutations	320 patients	Not reported	Next generation sequencing; pyrosequncing	Archival tumour tissue used	Test failures
Walthier 2012	Conference abstract	US	Multi-cancer gene testing for profiling solid tumours	Method development and experience of a single testing facility	Not applicable	Not reported	Parallel RT-PCR; Taqman array system; pyrosequencing	Not specified whether testing was on newly acquired, archive tissue or either	Estimated TAT_O
Wagle 2013	Conference abstract	US	Multi-cancer gene testing in various tumour types	Method development; feasibility study	Tissues from 15 patients	Not reported	Whole exome sequencing	Archive FFPE tissue,	TAT_{RR}
Hagermann 2015	Full journal article	US	Targeted sequencing of 23 genes in NSCLC	Feasibility study of routine targeted gene profiling; single testing centre	381 consecutive samples	Mar 2012-Oct 2013	Next generation sequencing	Archival FFPE tissues	Test failures TAT_O
Melchior 2015	Full journal article	Multi-national; 6 centres	BRAF mutation testing in malignant melanoma	Evaluation of test performance compared to original assessments made by several routine	148 left over samples	Not reported	RT-PCR (Idylla)	Reviewed archive FFPE tissue	Test failures TAT_{RT}

Lead author/Year	Citation type	Country	Diagnostic test	Context/Study type	Patients/Cases /Tests/requests	Date	Test method(s)	Use of archive tissue	Outcomes reported potentially relevant to this submission
				reference methods					

Abbreviations: HER2, human epidermal growth factor receptor 2; KRAS, Kirsten rat sarcoma; mCRC, metastatic colorectal cancer; NSCLC, non-small cell lung cancer; PCR, polymerase chain reaction RT, real time TATo = Overall turnaround time from ordering of test to reporting of test result; includes time of retrieval and review of archival tissue where applicable; TAT_{RS} = Time from ordering of test to receipt of sample at test facility, includes time of retrieval and review of archival tissue where applicable; TAT_{RR}= Time from receipt of sample at test facility to reporting of test result

B3.5 OUTCOMES MEASURES AND ANALYSES

CAVEAT

The data presented in Section B of the assessment are diverse in terms of the nature of the tests and 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 collections. This diversity presents potential uncertainty regarding the applicability of the study outcomes to the setting relevant to the proposed service.

The available data do not compare between scenarios which do and do not include the review process. This is because retrieval and review of archival tissues as a service is already generally accepted practice (PASC Outcomes on Protocol 1331). These data provide an indication of the technical outcomes of the testing procedure that may be "worsened" should review of samples not be undertaken or not adequately reimbursed.

TEST TURNAROUND TIMES

Turnaround times are variously reported as the overall turnaround time from ordering of test to reporting of test result (TAT_O); the turnaround time from ordering of test to receipt of sample at test facility (TAT_{RS}) and the turnaround time from receipt of sample at test facility to reporting of test result (TAT_{RR}). Importantly, TAT_O and TAT_{RS} will include the time taken to retrieve and review of archival tissue where this is applicable.

A TAT_{RS} of greater than 7 days is significant as this is longer than would be reimbursed in the proposed service.

According to Canadian and US guidelines, the maximum acceptable TAT_{RR} for KRAS mutation testing in mCRC and for EGFR mutation and ALK translocation testing in lung cancer is 10 working days (Aubin et al 2011; CAMP 2015; Lindeman et al 2013). European consensus on external quality assessment (EQA) in molecular pathology also suggest 10 working days as generally acceptable "The turnaround time, as defined by the EQA provider, should reflect the common clinical situation. Mostly a turnaround time of 10 working days is used for EQA samples…" (van Krieken et al, 2013).

Combined these suggests 15 working days or 3 weeks can be considered as an acceptable maximum for TAT_O.

KRAS MUTATION TESTING

Table 17 and Figure 8 summarise reported median turnaround times for KRAS mutation testing undertaken as a requested or routine pathology service with a view of treatment management of patients with mCRC. Median TAT_O was reported in 9 studies and ranged from 7 to 24 days. Of these only 5 studies reported a median TAT_O of 15 days or less. Median TAT_{RS} was reported in four studies and ranged from 5 to 19 days with three of the studies reported a median of 7 days or less. Median TAT_{RR} was reported in three studies, with median turnaround times of 6, 9 and 11 days.

Table 17 Median turnaround times for KRAS mutation testing undertaken as a requested or routine pathology service with a view of treatment management of patients with mCRC

First author/year	Country	Median turnaround time (days) [Range] *Unless stated otherwise* **TAT O**	Median turnaround time (days) [Range] *Unless stated otherwise* **TAT RS**	Median turnaround time (days) [Range] *Unless stated otherwise* **TAT RR**	Testing includes some/ all archival tissue
Reddy 2010	US	13	7		Not specified
Ciardiello 2011	Eur 2010 data	10			Not specified
	Latin Am 2010 data	15			Not specified
	Asia 2010 data	7			Not specified
Bibeau 2012	France	24			Yes
Lapeyrere 2012	France	15 [7-78] (IQR 12-21)	6[a]	9 [1-61] (IQR 7-11)	Yes
Chretien 2013	France	Mean 10.5 (7.0) reducing to 8.5 (3.3)			Not specified
Lievre 2013	France	19	6 [1-121]	11	Yes
Scott 2014	Australia	17 [0-191]			Yes
Lievre 2015	France	20			Yes
Lowe 2016	US		19 [IQR:1-303]	7[IQR:5-13]	Not specified

Abbreviations: IQR, interquartile range;
TAT= Turnaround time; TATo = Overall turnaround time from ordering of test to reporting of test result; includes time of retrieval and review of archival tissue where applicable; TAT_{RS} = Time from ordering of test to receipt of sample at test facility, includes time of retrieval and review of archival tissue where applicable; TAT_{RR}= Time from receipt of sample at test facility to reporting of test result.

a. Median 4 days [range 0-54] (IQR 0-8) from the test request to retrieving the sample from the archive and a median 2 days [range 0-22] (IQR 1-5) between sending sample out from source laboratory and its receipt at the testing facility.

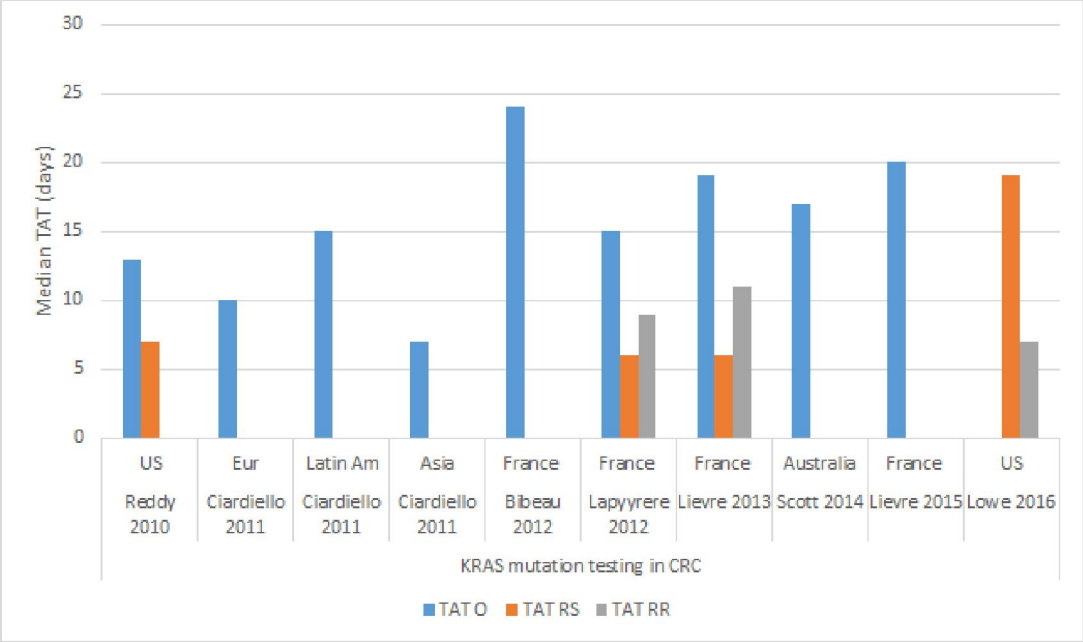

Figure 8 **Median turnaround times for KRAS mutation testing undertaken as a requested or routine pathology service with a view of treatment management of patients with mCRC**

IQR, interquartile range; TAT= Turnaround time; TATo = Overall turnaround time from ordering of test to reporting of test result; includes time of retrieval and review of archival tissue where applicable; TATRS = Time from ordering of test to receipt of sample at test facility, includes time of retrieval and review of archival tissue where applicable; TATRR= Time from receipt of sample at test facility to reporting of test result.

A study with the greatest applicability to this assessment is that of Scott et al, 2014 which reported TAT data based on an audit of KRAS mutation testing in four of nine major molecular pathology service providers in Australia. Results from this study are presented in Figure 9and Figure 10. Median TAT_O was between 2-3 weeks; median TAT_{RS} was 1 to 2 weeks and median TAT_{RR} was also between 1 to 2 weeks.

The study found for almost 30% of cases, more than 2 weeks (10 working days) elapsed before the sample was received by the testing laboratory. Upon receipt of the sample, a test result was produced within 2 weeks (10 working days) for 85% of cases (Figure 9). A result was available within 1 week for less than 10% of cases, while for 20.2% of cases the overall TAT was longer than 4 weeks (20 working days) (Figure 10).

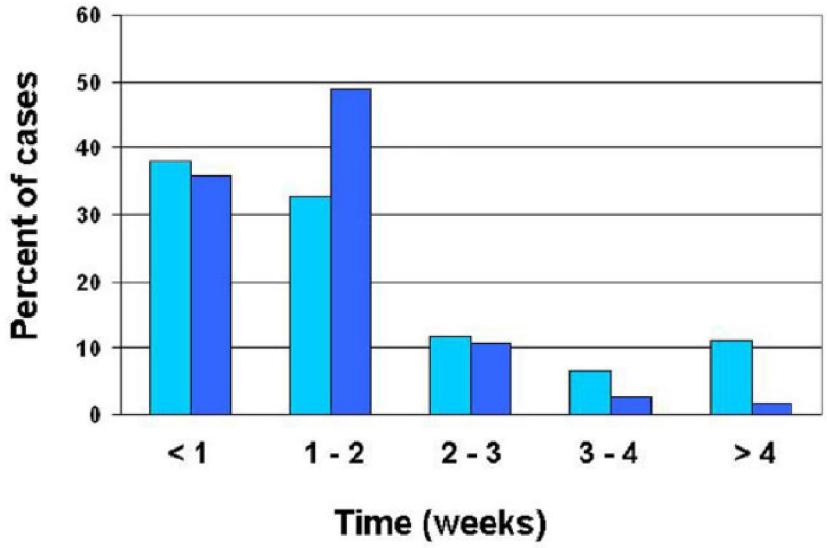

Figure 9 **Time elapsed between ordering of the KRAS test and reception of the sample in the test laboratory (TAT_{RS} light shading), and between reception of the sample and reporting of the KRAS mutation test result (TAT_{RR} dark shading).**

The data shown is for 4 of the 9 test sites for which this information was made available.

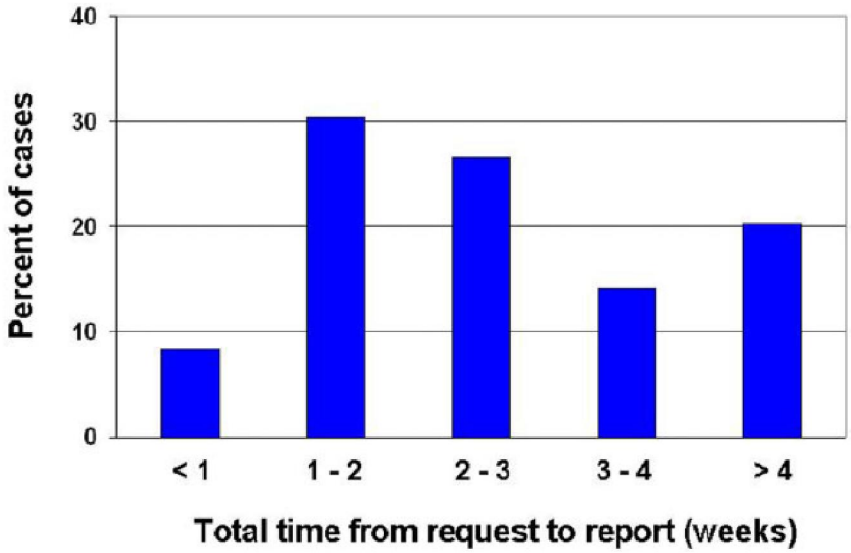

Figure 10 **Overall turnaround time (TAT_O) between ordering of the KRAS test and reporting of the test result.**

The data shown is for 4 of the 9 test sites for which this information was made available.

EGFR MUTATION TESTING

Table 18 and Figure 11Figure 8 summarise reported median turnaround times for EGFR mutation testing undertaken as a requested or routine pathology service with a view of treatment management of patients with NSCLC. Median TAT_O was reported in 8 studies and ranged from 9 to 38 days. Of these only 5 studies reported a median TAT_O of 15 days or less. Median or mean TAT_{RS} was reported in two studies (median 7 days; mean 4.9 days). Median TAT_{RR} was reported in 2 studies, both with median turnaround times of 11 days.

Table 18 **Median turnaround times for EGFR mutation testing undertaken as a requested or routine pathology service with a view of treatment management of patients with NSCLC**

First author/year	Country	Median turnaround time (days) [Range] *Unless stated otherwise* **TAT O**	Median turnaround time (days) [Range] *Unless stated otherwise* **TAT RS**	Median turnaround time (days) [Range] *Unless stated otherwise* **TAT RR**	Testing includes some/ all archival tissue
Gracia 2011	Spain	9.7			Not specified
	Spain on-site	8.5			
	Centralised	15.3			
Leary 2012	UK	Mean: 17.8	Mean: 4.9		Not specified
Tsao 2011	Canada		7	11	Yes
Raetskaya-Solntseva 2012	US pre-reflex	38			Yes
	US post reflex	21			Yes
Baldotto 2013	Brazil	21 improving to 5			Not specified
Ellis 2013	Canada	18 [15-26]	7	11	Not specified
Arriola 2014	Spain	9			Not specified
Janssens 2014	Belgium On-site	10 [3-37]			No
	Belgium Central	9 [3-27]			No

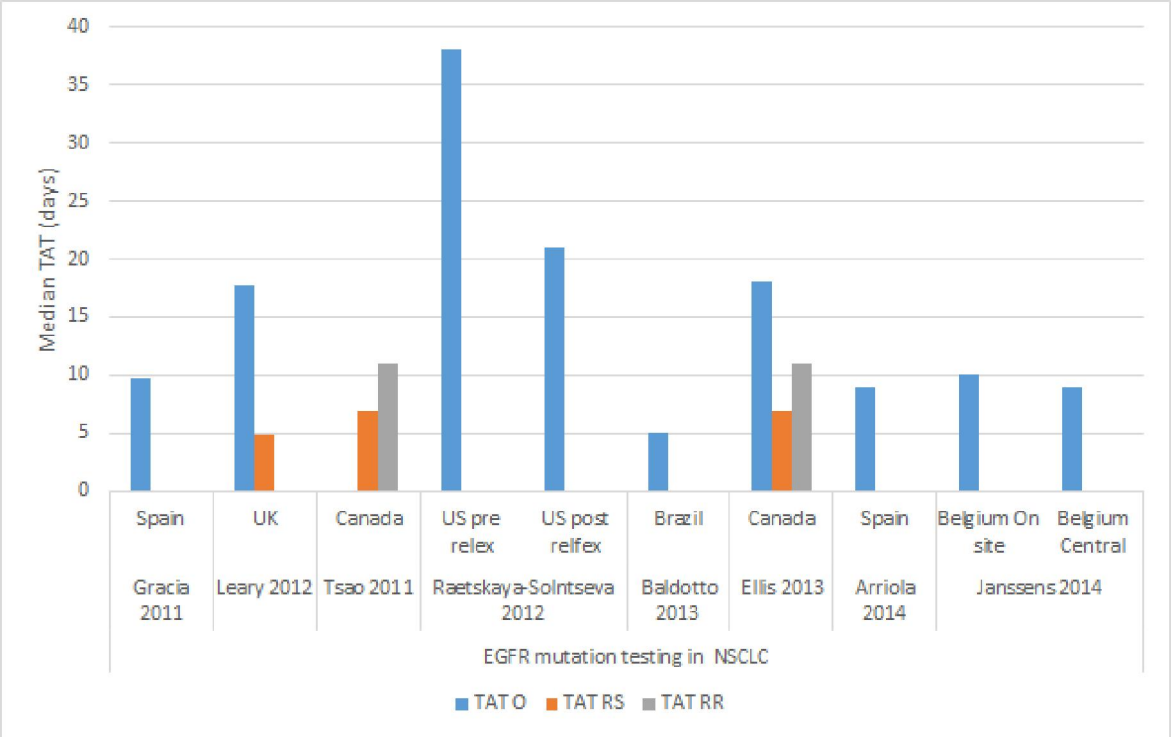

Figure 11 **Median turnaround times for EGFR mutation testing undertaken as a requested or routine pathology service with a view of treatment management of patients with NSCLC**

EGFR MUTATION AND ALK TRANSLOCATION TESTING

Table 19 and Figure 12 summarise reported median turnaround times for EGFR mutation with subsequent ALK testing undertaken as a requested or routine pathology service with a view of treatment management of patients with NSCLC. Median TAT_O was reported in 3 studies and ranged from 12 to 61 days. Only one study reported a median TAT_O of 15 days or less. None of these studies reported TAT_{RS} or TAT_{RR}.

Table 19 **Median turnaround times for EGFR mutation and ALK translocation testing undertaken as a requested or routine pathology service with a view of treatment management of patients with NSCLC**

First author/year	Country	Median turnaround time (days) [Range] *Unless stated otherwise*	Testing includes some/ all archival tissue
		TAT o	
Raetskaya-Solntseva 2012	US pre-reflex	61	Yes
	US post reflex	23	Yes
Cankovic 2013	US post streamline	61 improving to 12	Not specified
Lim 2015	Canada pre and post reflex	21 [1-679]	Yes

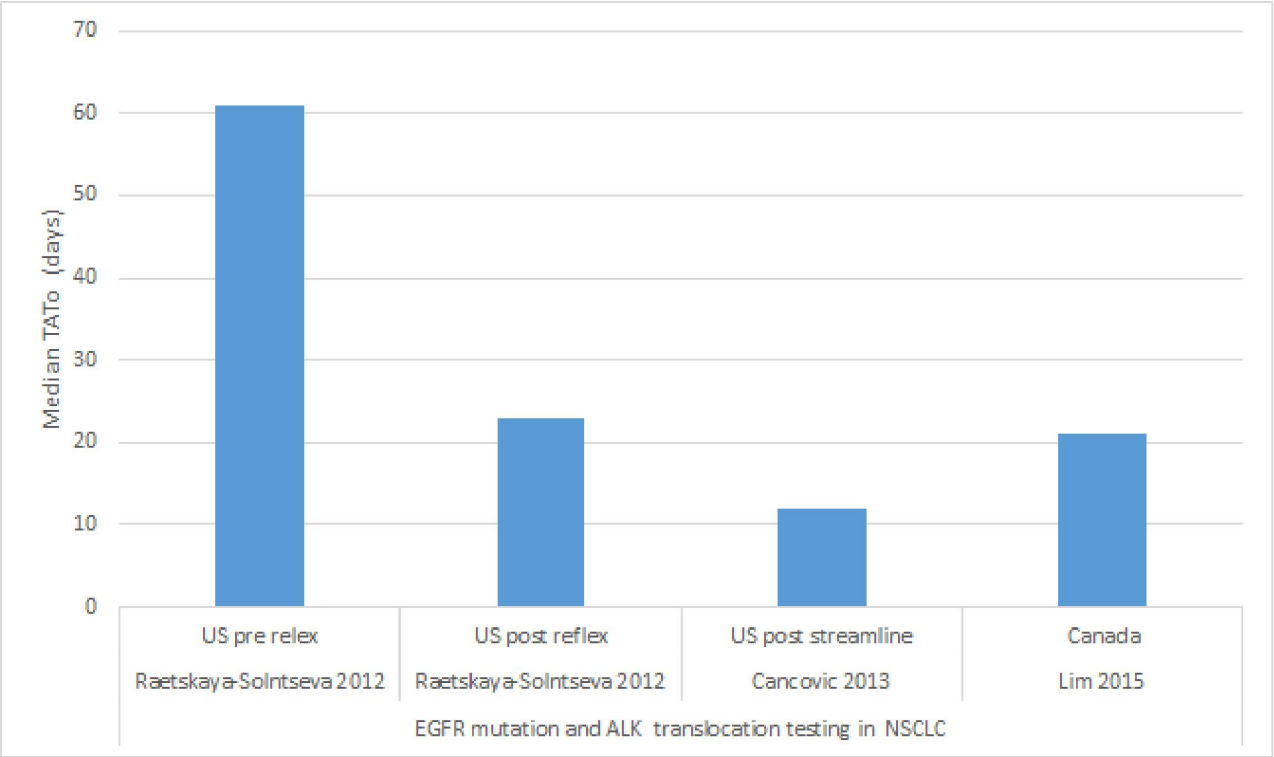

Figure 12 **Median turnaround times for EGFR mutation and ALK translocation testing undertaken as a requested or routine pathology service with a view of treatment management of patients with NSCLC**

Table 20 and Figure 13 summarise reported median turnaround times for HER2 testing undertaken as a requested or routine pathology service with a view of treatment management of patients with breast cancer. Median TAT_O ranged from 5 to 35 days with four studies reporting less than 15 days. With the exception of the Lim 2013 study, it is important to note these turnaround times are likely

to reflect the testing of newly acquired tissue rather than archival tissue, although this is not completely transparent from the information sources.

Table 20 Median turnaround times HER2 testing undertaken as a requested or routine pathology service with a view of treatment management of patients with breast cancer or gastro-oesophageal cancer

First author/year	Country	Median turnaround time (days) [Range] *Unless stated otherwise*		Testing includes some/ all archival tissue
		TAT_O	TAT_{RS}	
Fergusson 2009	UK	35[a]	13	Not specified
Goom 2012	UK	Range 19-31 days		No
Lim 2013	UK send out	8.27		Yes
	UK in-house	4.94		Yes
Shabaan 2014	UK	Mean 17 days improving to 12 days		Not specified
Steinmetz 2014	US post streamline	7 improving to 3		Not specified
Butt 2013	UK	10		Not specified

a. Median time includes operation to test result

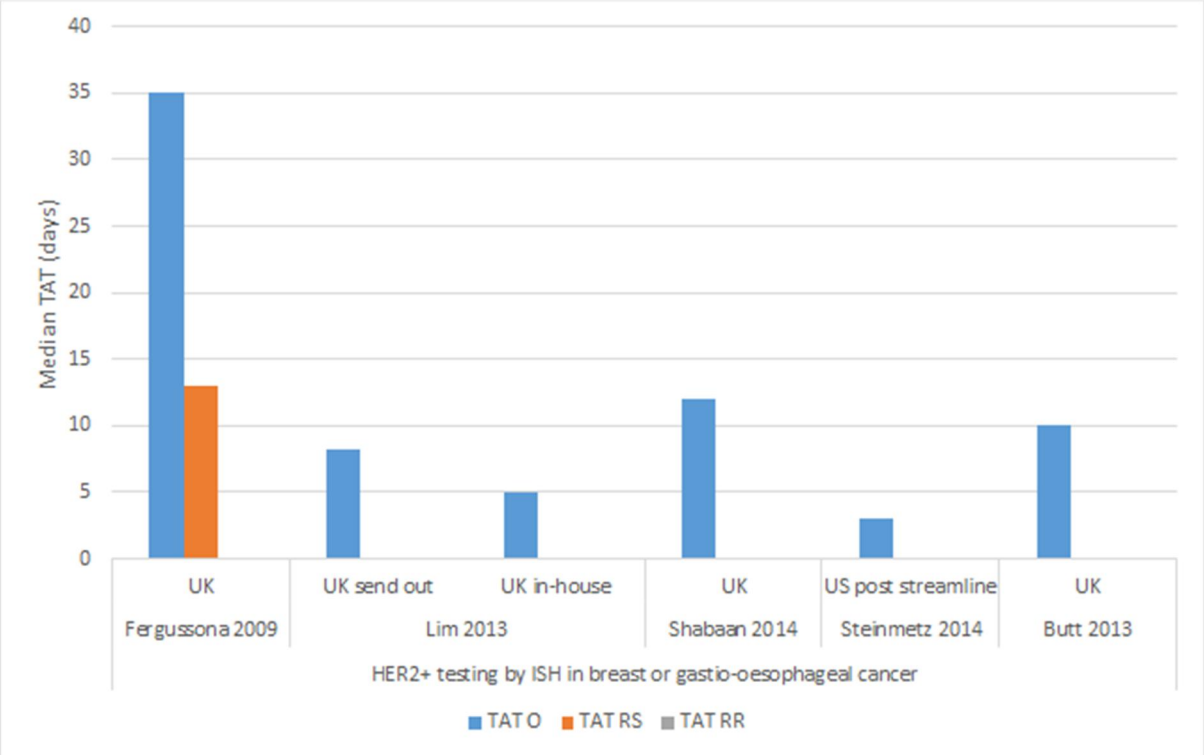

Figure 13 Median turnaround times HER2 testing undertaken as a requested or routine pathology service with a view of treatment management of patients with breast cancer or gastro-oesophageal cancer

Table 21 and Figure 14 summarise reported median turnaround times for multi-gene panel testing undertaken as a requested or routine pathology service with a view of treatment management of patients with various solid tumours. Median TAT_O was reported in 3 studies and ranged from 22 to

63 days. Median TAT_{RS} was reported in five studies and ranged for 6 days to 11 days. Median TAT_{RR} was reported in seven studies and ranged from 10 to 21 days.

Table 21 Turnaround times for gene panel testing

First author/year	Country	Median turnaround time (days) [Range] *Unless stated otherwise*			Testing includes some/ all archival tissue
		TAT_O	TAT_{RS}	TAT_{RR}	
Tran 2011	Canada	22 [15-35]		14	Yes
Morris 2014	US IHC		6	11	Not specified
	US Sequencing		6	12	Not specified
	US CIMP		6	20	Not specified
Schwaederle 2014	US	27[14-77]	11[1-58]		Yes
Smith 2014	US			15 [9-21]	Yes
Toulmonde 2014	France	63 [7-252]			Yes
Wagle 2013	US			16	Yes
Hagemann 2015	US		7[1-63]	21[9-15]	Yes

Abbreviations: IHC, immunohistochemistry; CIMP, CpG island methylator phenotype

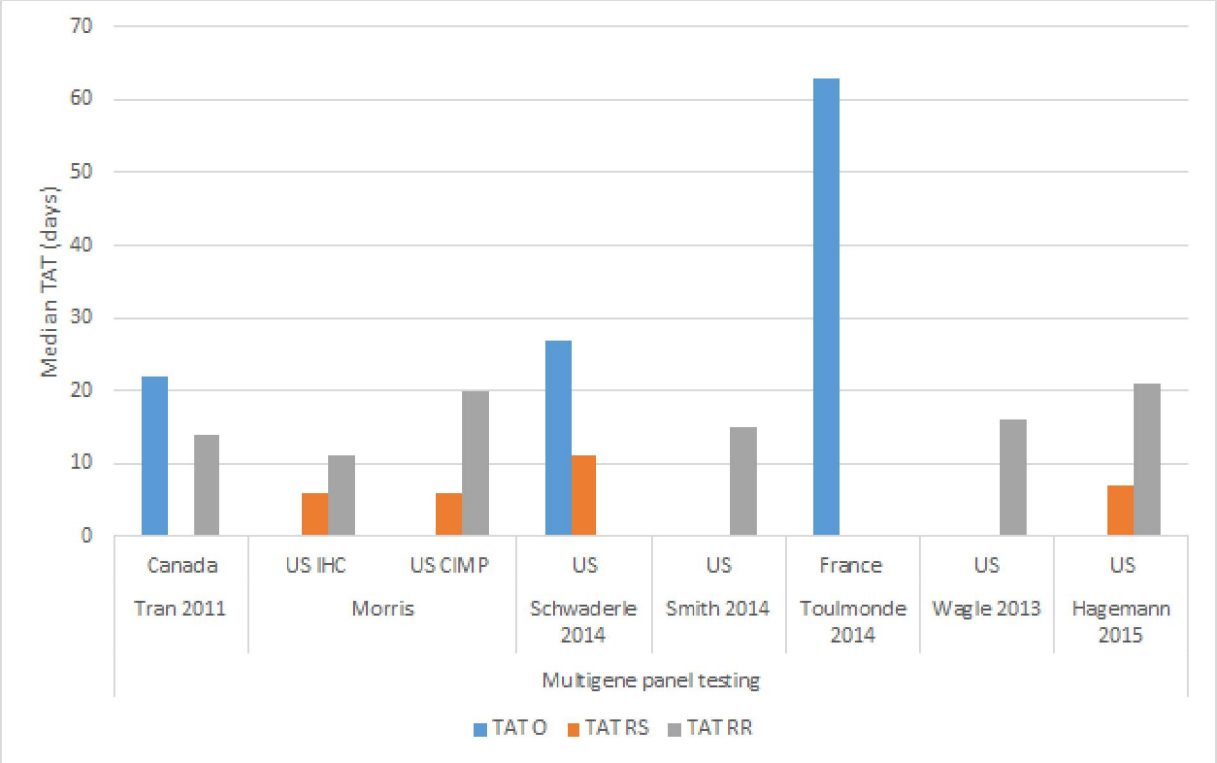

Figure 14 Turnaround times for gene panel testing

TEST FAILURE RATES

"NO TEST"

Test failure due to "No test" is where a tissue is unavailable for testing due the sample not being retrievable from the archive or, the tissue is retrievable but upon review, considered sub-optimal for testing due e.g., due to insufficient tissue quality or quantity. The significance of this measure is it provides an indication of the proportion of futile tests avoided because of the archival tissue review process and, provided no other more suitable archival tissue is available, identifies cases where re-biopsy might be considered.

Table 22 summarises data across the studies reporting the proportions of "No test" samples. Data from the studies of a single molecular diagnostic test undertaken as a requested or routine pathology service were limited to six studies. The proportions of 'no tests' ranged from 0.1% to 15.0%. From the limited data available and the limited tumour tissue types considered (colorectal, lung, gastro-oesophageal) lung tissue samples were most frequently found to be unsuitable for testing. Data from the four studies where multi-gene panel testing undertaken as a service on a variety of tumour tissues, the proportions of 'No tests' ranged from 4.6% to 12.4%. Data from studies where single molecular diagnostic testing or gene panel testing was undertaken for method development or research purposes the proportions of 'No tests' ranged from 0% to 41%.

"TEST WITHOUT RESULT"

Test failure due to "Test without result" is where, on review, an archival tissue sample has been deemed suitable for testing, however, on subsequent analysis the sample has failed to yield an interpretable result, for example due to there being an insufficient quantity of extractable DNA or the DNA being degraded. The significance of this measure is it provides an indication of the proportion of futile tests which cannot be avoided because of the archival tissue review process and, provided no other more suitable archival tissue is available, further cases where re-biopsy might be considered.

Table 23 summarises data across the studies reporting the proportions of "Test without result". Data from the studies of a single molecular diagnostic test undertaken as a requested or routine pathology service were limited to eight studies. The proportions of 'Test without result' ranged from 0.3% to 15.9%, with the majority of studies recording between 0.3% and 3.0%. Data from the three studies where multi-gene panel testing undertaken as a service on a variety of tumour tissues, the proportions of 'Test without result' were 2.0 %, 2.2% and 14.3%, with the highest proportion with a 'Test without result' based on a preliminary result set involving very few tested samples. Data from studies where single molecular diagnostic testing or gene panel testing was undertaken for method development or research purposes the proportions of 'Test without result' ranged from 3.1% to 18.2%.

"NO RESULT – REASON NOT SPECIFIED"

Table 24 summarises data from seven studies reporting test failures, but where the reason for the failure has not been specified. Regardless of the study type, the proportion of cases where there was "No result – reason unspecified" ranged from 5% to 56% and in the majority (5/7) of studies, the proportion with "No result – reason unspecified" was less 15%. Only one of these studies was of diagnostic testing conducted in clinical practice and in this study, test failures were reported as 18.8% in the first year, improving to 5.0% in the second year.

Table 22 Sample not tested due no or sub-optimal tissue

Test	First author/years	Country	Cases	Sample/Test request	Not tested		Percentage "No Test" due to no or sub-optimal tissue
					No sample	Sub-optimal sample	
Single molecular diagnostic testing undertaken as a requested or routine pathology service with a view of treatment management							
KRAS	Bibeau 2012	France		329	3		0.9%
KRAS	Lievre 2013	France	538	433	23		5.3%
EGFR	Gracia 2011	Spain		1009		68	6.7%
EGFR	Tsao 2011	Canada		1869	153	128	15.0%
EGFR	Ellis 2013	Canada		2104	106	145	11.9%
EGFR	Janssens 2014	Belgium		107		3	2.8%
HER2	Butt 2013	UK	844	833	11		1.3%
Gene panel testing of tumours, with a view of treatment management or placing patients into early phase clinical trials							
Multi-gene	Bedard 2013	Canada	485	485		24	4.9%
Multi-gene	Takahashi 2013	Japan	105	105		13	12.4%
Multi-gene	Yardley 2013	US		101		8	7.9%
Multi-gene	Morris 2014	US	400	400		32	8.0%
Single biomarker testing undertaken as part of diagnostic test method development, assessment of test performance or tumour characterisation for research purposes							
EGFR, ALK, BRAF & KRAS	Halblass 2011	Germany	88	88		8	9.1%
EGFR	Subramonia 2012	US		64		18	28.1%
HER2	Madrid 2004	Philippines		160			0.0%
HER2	Penault-Llorca 2008	France	710	710	293		41.3%
Genomic panel testing undertaken as part of method development, assessment of test performance or tumour characterisation for research purposes							
Multi-gene	Hagermann 2015	US	381	325		78	24.0%

Table 23 Sample tested but no result

Test	First author/years	Country	Samples tested	Tested but no result				Percentage "Test without result"
				Due to **insufficient** DNA	Due to degraded DNA	Due to other reasons	Total tested but with no result	
Single molecular diagnostic testing undertaken as a requested or routine pathology service with a view of treatment management								
KRAS	Bibeau 2010	France	575	3	12	2	17	3.0%
KRAS	Ciardiello 2011	Eur 2010	1679				70	4.2%
		Latin Am 2010	679				47	6.9%
		Asia 2010	261				2	0.3%
KRAS	Bibeau 2012	France	326				2	0.6%
KRAS	Chretien 2013	France	674		10		10	1.5%
EGFR&ALK	Lim 2013	Canada	126				20	15.9%
EGFR	Janssens 2014	Belgium	104	2				1.9%
HER2	Butt 2013	UK	833				9	1.1%
KRAS/BRAF/EGFR	Reddy 2010	US	104	16			16	15.4%
Gene panel testing of tumours, with a view of treatment management or placing patients into early phase clinical trials								
Multi-gene	Tran 2011	Canada	14	2				14.3%
Multi-gene	Bedard	Canada	461		9		9	2.0%
Multi-gene	Takahashi 2013	Japan	92				2	2.2%
Single biomarker testing undertaken as part of diagnostic test method development, assessment of test performance or tumour characterisation for research purposes								
KRAS	Carotenuto 2010	Italy	540		13			2.4%
EGFR & KRAS	Morgan 2011	Multi-national	146					<15%
EGFR & KRAS	Dingemans 2011	Netherlands	188		6		6	3.2%
Genomic panel testing undertaken as part of method development, assessment of test performance or tumour characterisation for research purposes								
Multi-gene	Hagermann 2015	US	209	32		6	38	18.2%
Multi-gene	Melchior 2015	Multi-national; 6 centres	148	8			8	5.4%

Table 24 No test result available; reasons not specified

Test	First author/years	Country	Samples	No test result; reason not specified	Percentage "No test result-reason not specified"
Single molecular diagnostic testing undertaken as a requested or routine pathology service with a view of treatment management					
KRAS	Leary 2012 year 1	UK	144	27	18.8%
	Leary 2012 year 2		755	38	5.0%
Single biomarker testing undertaken as part of diagnostic test method development, assessment of test performance or tumour characterisation for research purposes					
KRAS	Van Cutsem 2008	Multi-national	578	38	6.6%
KRAS	Dantes 2010	Germany	274	67	24.5%
KRAS, BRAF	Adulkareem 2010	UK	200	112	56.0%
EGFR, KRAS	Spigel 2010	US	128	16	12.5%
EGFR KRAS	Wu 2014	US	15	2	13.3%
Genomic panel testing undertaken as part of method development, assessment of test performance or tumour characterisation for research purposes					
Multi-gene	Peeters 2010	Multi- national	320	32	10%

RE-BIOPSY

Data regarding re-biopsy rates were reported in just two studies (Table 25). One study of EGFR and ALK testing in NSCLC reported a re-biopsy was possible in 84% of cases where testing had failed using archival tissue. Biomarker testing was possible of 94% of the re-biopsied tissue.

One study of multi-gene panel testing in various cancers reported testing in re-biopsy was undertaken in 23% of cases where testing had failed in archival tissues.

Table 25 Re-biopsy due to failed testing using archive tissue

Test	First author/year	Country	Failed tests n/N (%)	Re-biopsy n/N (%)	Adverse events n/N (%)	Insufficient tissue from re-biopsy n/N (%)
EGFR/ALK	Lim 2015	Canada	20/126 (15.9%)	16/20 (84%)	Not reported	1/16 (6%)
Multi-gene	Takahashi 2013	Japan	13/105 (12.3%)	3/13 (23%)	No serious AE	Not reported

B.4 INTERPRETATION OF EVIDENCE

B4.1 TEST TURNAROUND TIMES

Reimbursement for the proposed service requires a maximum TAT_{RS} of 7 days. According to published guidelines, the maximum acceptable TAT_{RR} for molecular diagnostic testing in cancer is 10 working days. Combined, these data suggest 15 working days or 3 weeks can be considered as an acceptable maximum for TAT_O.

The available data regarding turnaround times for the undertaking of molecular diagnostic testing indicate the consensus maximally accepted turnaround time is not being met in many cases. In these cases, TAT_O is longer than 3 weeks and TAT_{RR} is longer than 2 weeks. The reasons for variation are multi-factorial. The available data suggest the time taken from ordering of test to receipt of sample at test facility (TAT_{RS}), which includes time taken for the retrieval of archival material, contributes significantly to the overall test turnaround time and is frequently longer than the proposed reimbursement target time of 7 days.

Data from the Australian setting (Scott et al, 2014) in relation to KRAS mutation testing in clinical practice found, in the vast majority of cases (85%), upon receipt of sample at the testing facility, a test result was produced within the guideline maximally accepted time scale of 2 weeks. Yet a TAT_O of 3 weeks or longer was observed in more than 35% of cases and this was most attributed to a delay in when the sample was received by the testing laboratory (2 weeks or longer in approximately 30% of cases).

No study has investigated the impact on TAT_{RS} of providing a reimbursement incentive for the achieving retrieval and review within a time target. Nonetheless, the data do show the time for archive tissue retrieval to be greater than 7 days in a proportion of cases. Assuming reimbursement of the retrieve and review process will incentivise those cases to deliver within 7 days (as required

for reimbursement), then it follows the proposed intervention is superior to current practice in terms of TAT_{RS} and TAT_{O}. It should be noted, however, and MBS listing would involve reimbursing cases which would be delivered within the seven days with or without reimbursement. These costs will be incorporated within the economic evaluation to follow.

B4.2 TEST FAILURE RATES

The "No test" measure is indicative of the proportion of futile tests which could be avoided because of the archival tissue review process and, provided no other more suitable archival tissue is available, identifies cases where re-biopsy might be considered (before MBS incurs a fee for the test). The available data show variability in the proportion of tissues deemed on review as sub-optimal for testing. The reasons for the variation are likely to be multi-factorial.

The "test without result" measure may be considered indicative of the proportion of futile tests which cannot be avoided because of the archival tissue review process and, provided no other more suitable archival tissue is available, further cases where re-biopsy might be considered. Again, the available data show variability in the proportion of tissues which are deemed on review as suitable for testing yet fail to yield test results. Again, the reasons for this variation are likely to be multi-factorial.

The available data confirm prior review by a pathologist identifies a proportion of archival tissues as being sub-optimal for molecular diagnostic testing. However, a proportion of archival tissues deemed as suitable for testing will fail to yield results despite the prior review.

The available data do not compare between scenarios which do and do not include the review process. Nonetheless, the data do show sub-optimal archive tissue does exist and inclusion of the tissue review in the process can be assumed superior in that it should reduce the number of tests being conducted on sub-optimal tissue which in turn would reduce costs on futile tests and/or improve diagnostic accuracy.

B4.3 RE-BIOPSY

Available data regarding re-biopsy rates due to failed diagnostic testing are sparse. Based on the available data, not all failed tests result in re-biopsy and not all re-biopsies necessarily provide sufficient material for testing.

SECTION C TRANSLATION ISSUES

C.1 OVERVIEW

The clinical evaluation in Section B showed turnaround times for archival sample retrieval and review in current practice to be 7 days or greater days in approximately 60% of cases (Scott et al. 2014). The proposed intervention requires this turnaround time to be within seven days otherwise, the MBS fee is not payable.

Therefore, the proposed intervention can be considered superior to the "unfunded" comparator in terms of time taken for an optimal sample to be available for testing. As such, the purpose of the economic model is to quantify the cost and quality of life implications of this improved turnaround time and the appropriate form of economic evaluation is cost-utility analysis.

The DAP and subsequent PASC Outcomes on Protocol 1331 incorporate a number of other potential comparators:

- Retrieval without review
- No retrieval and patient referred directly for biopsy
- No retrieval, no test, and patient remains ineligible for PBS drug (receives BSC)

Without direct evidence confirming as such, the proposed intervention can nevertheless be assumed to be superior to each one of these comparators on at least one outcome as follows:

- Compared to retrieval without review:
    - Retrieve and review should reduce the number of tests being conducted on sub-optimal tissue which in turn would reduce costs on futile tests and/or improve diagnostic accuracy
- Compared to no retrieval and patient referred directly for biopsy:
    - Retrieve and review has time, cost and quality of life advantages for the patient
- Compared to no retrieval, no test, and patient remains ineligible for PBS drug:
    - Retrieve and review means those patients who would be eligible for the PBS drug go on to receive the efficacy, effectiveness and QALY gains associated with the PBS treatment

As such, cost-utility analysis is also the appropriate form of economic evaluation relative to each of these alternative comparators.

The economic evaluation is a modelled economic evaluation based on data presented in Section B of this assessment report. The PASC Outcomes on Protocol 1331 "noted that archiving and retrieval of pathology samples had already been fully disseminated, and current practice is to archive tissue for at least 10 years…" and that "the service had already become generally accepted practice". Furthermore, Section B noted that no studies or investigations have ever been made to determine

the effectiveness of reviewing the sample prior to testing. As such, essentially all the data in Section B reflects a circumstance where reviewing the sample has occurred.

As described above, the main purpose of the economic model is to quantify the cost and quality of life implications of improved turnaround time (assuming all else remains equal) which will occur should funding for retrieval and review be included on the MBS. However, the main difficulty in the economic evaluation of retrieve and review relative to the alternative comparators is not the therapeutic claims of superiority (as described above) but rather the magnitude of this superiority claim. For example, the proportion of the 60% of cases which currently take more than 7 days which will now take less than 7 days remains uncertain. To this end, the economic model relies on sensitivity analysis and threshold analysis to provide insight in to the extent of superiority required for the proposed retrieve and review item number to be deemed cost-effective.

C.2 APPLICABILITY TRANSLATION ISSUES

The data presented in Section B are disparate in terms of the tests, 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 collections. With the exception of data reported by Scott et al 2014 in relation to test turnaround times for KRAS testing in mCRC, the applicability of the presented to the Australian setting cannot necessarily be ascertained or guaranteed. Any formal data applicability assessment is considered infeasible. Nonetheless, these data do provide an indication of the technical outcomes of the testing procedure that may be "worsened" should proposed service involving the review of archival samples prior to testing not be undertaken or not adequately reimbursed.

C.3 EXTRAPOLATION ISSUES

The clinical evaluation covers a time period up until the test result is obtained. Therefore, there are no specific time-related extrapolation issues to consider in a pre-modelling study.

The downstream and future implications of the test result (in terms of false positives or false negatives) may have longer term implications. These implications are assessed as transformation issues and described within the structure of the decision analytic economic model presented in Section D.

C.4 TRANSFORMATION ISSUES

The transformation issues in the economic evaluation follow the linked evidence framework as outlined in Section B.2 (Table 26). That is, the implication of an absence of a review may lead to the potential for futile or inaccurate testing, or the implications for delayed testing may lead to the potential for disease progression before treatment can be initiated.

Table 26 Summary of links/transformations in the economic model

Alternative	Benefits of funded retrieval and review of sample	Transformation issue
Unfunded retrieve and review	Increases the number of samples reviewed within one week	Time savings lead to fewer "false negatives" because patients will be allocated to treatment in time (i.e. before disease progression)
Retrieve and no review of tissue sample	Reduces the number of tests being conducted on sub-optimal tissue (sample quality)	Cost savings Time savings
	Improves diagnostic accuracy and treatment allocation	Fewer false positives (more true negatives) leads to: Cost savings (drug avoided) QoL gains (toxicity avoided) Fewer false negatives (more true positives) leads to: Additional costs (drug used) QoL gains (drug efficacy)
No retrieval and patient referred directly for biopsy	Reduces the number of biopsies being conducted	Cost savings QoL gains from biopsies avoided
No retrieval and no new biopsy, no test	Patient remains ineligible for PBS drug and receives BSC. Patients who were truly eligible, but could not be identified because there was no retrieval or no new biopsy and therefore couldn't have the diagnostic test, will forgo any potential QALYs gained	More true positives Additional costs (drug used) QoL gains (drug efficacy)

The transformation issues require determination the cost and QoL implications of the relevant PBS treatment. These cost and QoL implications have the potential to vary considerably across the different populations and settings in which archive tissue is reviewed and the corresponding tests undertaken. In order to estimate the implications and opportunity costs of treatment allocation, it was necessary to determine the incremental costs and incremental benefits of the treatment(s) being initiated after a molecular diagnostic test. This means it is theoretically necessary to undertake an economic evaluation of retrieve and review in each of the current and potential future settings in which archive tissue is used. To avoid re-evaluating the cost-effectiveness of all the indications with co-dependant technologies as outlined in the Protocol, a search of relevant PBAC PSDs across these indications and their co-dependent molecular diagnostic tests (Table 27) was conducted. The aim was to identify PFS data to assess the implications for delayed testing and to identify incremental costs and incremental benefits of the treatment(s) being initiated after a molecular diagnostic test to assess the implications for inaccurate testing. A list and details of the PSDs identified of treatments recommended in the indications are summarised in Table 28. Economic outcomes are presented in Table 29.

Table 27 Indications and accompanying diagnostic tests and treatments

Diagnostic test (MBS Item)	Indication	Treatments
HER2 (73332)	breast cancer	Trastuzumab
BRAF V600 (73336)	unresectable stage III or stage IV metastatic cutaneous melanoma	Dabrafenib
EGFR+ (73337)	non-squamous non-small cell lung cancer	Erlotinib, Gefitinib
RAS (73338)	metastatic colorectal cancer	Cetuximab, Panitmumab
ALK+, EGFR- (73341)	locally advanced or metastatic non-squamous non-small cell lung cancer	Crizotinib
HER2+ (73341)	metastatic adenocarcinoma of the stomach or gastro-oesophageal junction	Trastuzumab

Table 28 Survival outcomes reported in the identified PBAC PSDs

Source	Source trial	Intervention	Patients	PFS results	HR; p-value	OS results	HR; p-value
KRAS WT metastatic colorectal cancer 2nd line (cetuximab as monotherapy or combination with CHEMO)							
PBAC PSD Jul 2010	CO17 (Karapetis 2008)	cetuximab + CHEMO vs. BSC	WT	3.7 vs. 1.9 months	0.4 [0.3, 0.54]; <0.001	9.5 vs. 4.8 months	0.55 [0.41, 0.74]; <0.001
			MT	1.8 vs 1.8 months	0.99 [0.73, 1.35]; 0.96	4.5 vs. 4.6 months	0.98 [0.70, 1.37]; 0.89
RAS WT metastatic colorectal cancer 1st line (cetuximab combination with CHEMO)							
PBAC PSD Nov 2014	FIRE-3	cetuximab + FOLFIRI vs. bevacizumab + FOLFIRI	RAS WT	10.4 vs. 10.2 months	0.93 [0.74, 1.17]; 0.536	33.1 vs. 25.6 months	0.7 [0.53, 0.92]; 0.001
	CALGB/SWOG 50405	bevacizumab + FOLFIRI or FOLFOX vs. cetuximab + FOLFIRI or FOLFOX	RAS WT	NR	NR	31.2 vs. 32 months	0.9 [0.7, 1.1]; 0.4
	CALGB/SWOG 50405	bevacizumab + FOLFOX vs. cetuximab + FOLFOX	RAS WT	NR	NR	29.0 vs. 32.5 months	0.86 [0.6, 1.1]; 0.2
	CALGB/SWOG 50405	cetuximab + FOLFIRI vs. bevacizumab + FOLFIRI	RAS WT	NR	NR	35.2 vs. 32 months	1.1 [0.7, 1.6]; 0.7
KRAS WT metastatic colorectal cancer later line (panitumumab monotherapy or combination with FOLFIRI)							
PBAC PSD Mar 2013 Nov 2013	ASPECCT	panitumumab vs. cetuximab	KRAS WT	4.1 vs. 4.4 months	1.002 [0.882, 1.138]; NR	10.4 vs. 10 months	0.966 [0.839, 1.113]; 0.0007
	ITC; Trial 0181, EPIC	panitumumab + FOLFIRI vs. cetuximab via irinotecan	KRAS WT	NR	0.95 [0.66, 1.37]; NSS	not conducted	not conducted
	ITC; Trial 0408; Trial CO.17	panitumumab + FOLFIRI vs. cetuximab via BSC	KRAS WT	NR	1.13 [0.75, 1.68]; NSS	not conducted	not conducted
RAS WT metastatic colorectal cancer 1st line (panitumumab combination with FOLFOX)							
PBAC PSD Jul 2014 Mar 2015	PRIME	panitumumab + FOLFOX vs. FOLFOX	KRAS WT	10 vs. 8.6 months	0.80 [0.67, 0.95]; SS	23.9 vs. 19.7 months	0.88 [0.73, 1.06]; NSS
			RAS WT	10.8 vs. 8.6 months	0.73 [0.60, 0.88]; SS	25.8 vs. 20.2 months	0.77 [0.64, 0.94]; SS
			RAS M+	7.4 vs. 8.1 months	1.37 [0.90, 2.10]; NSS	17.1 vs. 17.8 months	1.39 [0.91, 2.13]; NSS
	PEAK	panitumumab + FOLFOX vs.	KRAS WT	10.9 vs. 10.1 months	0.84 [0.64, 1.11]; NSS	34.2 vs. 24.3 months	0.62 [0.44, 0.89]; SS

Source	Source trial	Intervention	Patients	PFS results	HR; p-value	OS results	HR; p-value
		bevacizumab + FOLFOX	RAS WT	13 vs. 10.1 months	0.66 [0.46, 0.95]; SS	41.3 vs. 28.9 months	0.63 [0.39, 1.02]; NSS
			RAS M+	8.4 vs. 8.8 months	1.13 [0.63, 2.05]; NSS	27.0 vs. 16.6 months	0.41 [0.19, 0.87]; SS
	ITC	panitumumab + FOLFOX vs. cetuximab (non-inferiority)	NR	NR	NR	NR	NR
EFGR M+ locally advanced or metastatic NSCLC 1st line (erlotinib monotherapy)							
PBAC PSD Jul 2012 Jul 2013	EURTAC	erlotinib vs. platinum-based CHEMO[a]	EGFR+	Difference 5.3 months	0.34 [0.23, 0.49]; <0.001	NR	NSS
EFGR M+ locally advanced or metastatic NSCLC 1st line (gefitinib monotherapy)							
PBAC PSD Nov 2010 Nov 2012 Jul 2013	IPASS	gefitinib vs. platinum-based CHEMO[b]	ITT	5.7 vs. 5.8 months	0.74 [0.65, 0.85]; <0.001	18.8 vs. 17.4 months	0.90 [0.79, 1.02]; >0.05
			EGFR M+	9.5 vs. 6.3 months	0.48 [0.36, 0.64]; <0.001	21.6 vs. 21.9 months	1.00 [0.76, 1.33]; 0.99
			EGFR M-	1.5 vs. 5.5 months	2.85 [2.05, 3.98]; <0.001	11.2 vs. 12.7 months	1.18 [0.86, 1.63]; 0.309
	First-SIGNAL	gefitinib vs. platinum-based CHEMO[c]	EGFR ITT	5.8 vs. 6.4 months	1.20 [0.394, 1.52]; 0.138	22.3 vs. 22.9 months	0.93 [0.72, 1.21]; 0.604
			EGFR M+	8.0 vs.6.3 months	0.54 [0.27, 1.10]; 0.086	27.2 vs. 25.6 months	1.04 [0.5, 2.18]; NR
			EGFR M-	2.1 vs. 6.4 months	1.42 [0.82, 2.47]; 0.226	18.4 vs. 21.9 months	0.88 [0.64, 1.21]; NR
	NEJ002	gefitinib vs. platinum-based CHEMO[b]	EGFR M+	Difference 5.4 months	0.30 [0.22, 0.41]; SS	NR	NRN
	WJTOG3405	gefitinib vs. platinum-based CHEMO[d]	EGFR M+	Difference 2.9 months	0.49 [0.34, 0.71]; SS	NR	NR
ALK+ locally advanced or metastatic NSCLC 2nd Line (crizotinib monotherapy)							
PBAC PSD Nov 2013 Mar 2014 Nov 2014	A8081007	crizotinib vs. CHEMO[e]	ALK+	7.7 vs. 3.0 months	0.487 [0.371, 0.638]; SS	20.3 vs. 22.8	1.021 [0.677, 1.540]; NSS
	A8081007	crizotinib vs. pemetrexed	ALK+	7.7 vs. 4.2 months	0.589 [0.431, 0.804]; SS	NR	NR
	A8081007	crizotinib vs. docetaxel	ALK+	7.7 vs. 2.6 months	0.298 [0.207, 0.428]; SS	NR	NR
HER2+ positive advanced adenocarcinoma of the stomach or gastro-oesophageal junction 1st line (trastuzumab combination with CHEMO)							
PBAC PSD Jul 2011	ToGA (Bang et al)	trastuzumab +CHEMO[f] vs. CHEMO[f]	HER2+	6.7 vs. 5.5 months	0.71 [0.59, 0.85]; SS	13.8 vs. 11.1 months	0.74 [0.60, 0.91]; SS

Source	Source trial	Intervention	Patients	PFS results	HR; p-value	OS results	HR; p-value
Nov 2012 July 2015							
HER2+ early breast cancer following surgery (trastuzumab combination with chemotherapy)							
PBAC PSD July 2006	HERA trial; US NCI trial B-31; US NCI trial N9831; FinHer trial; BCIRG 006	trastuzumab plus adjuvant chemo vs. placebo	HER2+	NR	NR	NR	0.66 [0.47, 0.91]; 0.0115
HER2+ locally advanced breast cancer (neoadjuvant trastuzumab therapy combination with chemotherapy)							
PBAC PSD July 2012	ITC	neoadjuvant trastuzumab + CHEMO vs. adjuvant trastuzumab + CHEMO	HER2+	NR	NR	NR	NR
HER2+ metastatic breast cancer 1st line (trastuzumab combination with a taxane)							
PBAC PSD Nov 2014	M77001	trastuzumab + docetaxel vs. docetaxel	HER2+	NR	NR	31.2 vs. 22.7 months	Redacted; NSS
BRAF V600+ advanced or metastatic melanoma 1st line (dabrafenib monotherapy)							
PBAC PSD Mar 2013 Jul 2013	BREAK-3	dabrafenib vs. dacarbazine	BRAF V600+	6.9 vs. 2.7 months	0.37 [0.23, 0.58]; SS	OS not mature	0.75 [0.44, 1.29]; NSS

a. cisplatin or carboplatin with either docetaxel or gemcitabine
b. carboplatin and paclitaxel
c. cisplatin and gemcitabine
d. cisplatin plus docetaxel
e. pemetrexed or docetaxel
f. cisplatin and fluoropyrimidine (capecitabine or 5-FU)

Table 29 Economic outcomes reported in the identified PBAC PSDs

Source	Source trial	Intervention	Patients	Incremental cost	Incremental benefit	Incremental QALY	Cost/QALY
KRAS WT metastatic colorectal cancer 2nd line (cetuximab as monotherapy or combination with CHEMO)							
PBAC PSD Jul 2010	CO17 (Karapetis 2008)	cetuximab + CHEMO vs. BSC	WT	$15,000	0.39 LYG	0.25 QALYs	$45,000-$75,000
RAS WT metastatic colorectal cancer 1st line (cetuximab combination with CHEMO)							
PBAC PSD Nov 2014	FIRE-3	cetuximab + FOLFIRI vs. bevacizumab + FOLFIRI	RAS WT	Redacted	Redacted	Redacted	Redacted
	CALGB/SWOG 50405	bevacizumab + FOLFIRI or FOLFOX vs. cetuximab + FOLFIRI or FOLFOX	RAS WT				
	CALGB/SWOG 50405	bevacizumab + FOLFOX vs. cetuximab + FOLFOX	RAS WT				
	CALGB/SWOG 50405	cetuximab + FOLFIRI vs. bevacizumab + FOLFIRI	RAS WT				
KRAS WT metastatic colorectal cancer later line (panitumumab monotherapy or combination with FOLFIRI)							
PBAC PSD Mar 2013 Nov 2013	ASPECCT	panitumumab vs. cetuximab	KRAS WT	NR	NR	NR	NR
	ITC; Trial 0181, EPIC	panitumumab + FOLFIRI vs. cetuximab via irinotecan	KRAS WT	NR	NR	NR	NR
	ITC; Trial 0408; Trial CO.17	panitumumab + FOLFIRI vs. cetuximab via BSC	KRAS WT	NR	NR	NR	NR
RAS WT metastatic colorectal cancer 1st line (panitumumab combination with FOLFOX)							
PBAC PSD Jul 2014 Mar 2015	PRIME	panitumumab + FOLFOX vs. FOLFOX	KRAS WT	Redacted	Redacted	Redacted	$45,000-$75,000
	PEAK	panitumumab + FOLFOX vs. bevacizumab + FOLFOX	KRAS WT	Redacted	Redacted	Redacted	DOMINAT
	ITC	panitumumab + FOLFOX vs. cetuximab (non-inferiority)	NR	NR	NR	NR	NR
EFGR M+ locally advanced or metastatic NSCLC 1st line (erlotinib monotherapy)							
PBAC PSD Jul 2012 Jul 2013	EURTAC	erlotinib vs. platinum-based CHEMO[a]	EGFR+	NR	NR	NR	$45,000-$75,000

Source	Source trial	Intervention	Patients	Incremental cost	Incremental benefit	Incremental QALY	Cost/QALY
EFGR M+ locally advanced or metastatic NSCLC 1st line (gefitinib monotherapy)							
PBAC PSD Nov 2010 Nov 2012 Jul 2013	IPASS	gefitinib vs. platinum-based CHEMO[b]	EGFR M+	NR	0.152 LYG	NR	$45,000-$75,000
	First-SIGNAL	gefitinib vs. platinum-based CHEMO[c]					
	NEJ002	gefitinib vs. platinum-based CHEMO[b]					
	WJTOG3405	gefitinib vs. platinum-based CHEMO[d]					
ALK+ locally advanced or metastatic NSCLC 2nd Line (crizotinib monotherapy)							
PBAC PSD Nov 2013 Mar 2014 Nov 2014	A8081007	crizotinib vs. CHEMO[e]	ALK+	NR	NR	NR	$45,000-$75,000
	A8081007	crizotinib vs. pemetrexed	ALK+				
	A8081007	crizotinib vs. docetaxel	ALK+				
HER2+ positive advanced adenocarcinoma of the stomach or gastro-oesophageal junction 1st line (trastuzumab combination with CHEMO)							
PBAC PSD Jul 2011 Nov 2012 July 2015	ToGA (Bang et al)	trastuzumab +CHEMO[f] vs. CHEMO[f]	HER2+	Redacted	Redacted	Redacted	$45,000-$75,000
HER2+ early breast cancer following surgery (trastuzumab combination with chemotherapy)							
PBAC PSD July 2006	HERA trial; US NCI trial B-31; US NCI trial N9831; FinHer trial; BCIRG 006	trastuzumab plus adjuvant chemo vs. placebo	HER2+	NR	NR	NR	$45,000-$75,000
HER2+ locally advanced breast cancer (neoadjuvant trastuzumab therapy combination with chemotherapy)							
PBAC PSD July 2012	ITC	neoadjuvant trastuzumab + CHEMO vs. adjuvant trastuzumab + CHEMO	HER2+	NR	NR	NR	NR
HER2+ metastatic breast cancer 1st line (trastuzumab combination with a taxane)							
PBAC PSD Nov 2014	M77001	trastuzumab + docetaxel vs. docetaxel	HER2+	NR	NR	NR	$45,000-$75,000
BRAF V600+ advanced or metastatic melanoma 1st line (dabrafenib monotherapy)							

Source	Source trial	Intervention	Patients	Incremental cost	Incremental benefit	Incremental QALY	Cost/QALY
PBAC PSD Mar 2013 Jul 2013	BREAK-3	dabrafenib vs. dacarbazine	BRAF V600+	NR	NR	NR	$45,000-$75,000

a. cisplatin or carboplatin with either docetaxel or gemcitabine
b. carboplatin and paclitaxel
c. cisplatin and gemcitabine
d. cisplatin plus docetaxel
e. pemetrexed or docetaxel
f. cisplatin and fluoropyrimidine (capecitabine or 5-FU)

For the purposes of the economic evaluation a single population indication is used; mCRC. The listing of cetuximab as monotherapy or in combination with irinotecan based therapy (also BSC), following failure of first-line chemotherapy for treatment of patients with KRAS wild-type metastatic colorectal cancer (mCRC) was recommended by the PBAC (PBAC PSD July 2010). This recommendation was primarily based on the evidence in the CO17 trial (Karapetis et al 2008) for the second line setting of metastatic colorectal cancer (mCRC). Among the PSDs identified, this recommendation was the only PSD that provided the information on the IC and IB of treatment as well as PFS data. Therefore, the economic evaluation will be using these values as a proxy for all the other molecular diagnostic tests in the other 5 indications. In this sense, despite the economic evaluation being an mCRC model, it has a reasonable level of applicability to the other indications which, according to information presented in the PSDs, were all recommended for listing with a cost/QALY within the range of $45,000-$75,000; cetuximab for metastatic colorectal cancer was recommended with an ICER of $60,000 cost/QALY (Confidential Special Pricing Arrangements (SPA) preclude this assumption from being verified).

Furthermore, it is estimated that, in total, 7,374 episodes of the retrieval and review of archival tissue are performed in relation to the existing six pathology tests considered in the current analysis, the majority (47%) of which are estimated to be performed for RAS testing in patient with mCRC (See Section E.2).

IMPLICATIONS OF INACCURATE TESTING

In the scenario where diagnostic testing is undertaken without review of archival tissue by a pathologist prior to molecular diagnostic testing, there is an increased likelihood of a retrieved archived sample being of sub-optimal condition for testing (e.g., due to insufficient tumour material; poor quality sample etc.) resulting in an increased likelihood of futile testing (i.e., where no result is obtained) or inaccurate testing. In the circumstance of futile testing, the health system will accrue the cost of the test, but the patient will still require another biopsy to obtain a tissue in optimal condition for molecular diagnostic testing. This circumstance is included within the economic model structure.

Inaccurate tests can lead to false positive or false negative allocations to treatment. A false positive result is where the test was incorrect in identifying the presence of a mutation, therefore the patient would receive treatment that is not needed and may experience drug toxicities. Patients wrongly assigned the targeted treatment would get the incremental cost of the treatment and possible detrimental effects of the treatment but not the incremental benefit over standard treatment. A false negative result is where the test was incorrect in identifying no mutation, therefore the patient would not receive treatment that is needed and may consequently achieve a poorer survival outcome. Patients wrongly assigned no targeted treatment would not get the incremental cost but also would not get any incremental benefit over standard treatment.

The implications of false positive and false negative outcomes depend upon the incremental costs and benefits of the treatment being indicated (or otherwise). That is, the difference between a true

positive and a false negative are the incremental costs and incremental benefits accrued as a result of being assigned to PBS drug treatment. In this sense, the cost-effectiveness of a test (and by extension, review of the test sample) is limited by the cost-effectiveness of the treatment it is being used to initiate. Similarly, the difference between a true negative and a false positive result is the incremental cost and toxicity implications of futile treatment.

The July 2010 PBAC PSD for cetuximab was the only PSD that provided the information to determine the IC and IB of treatment. The economic model for the second line setting of metastatic colorectal cancer (mCRC) demonstrated an incremental overall survival benefit of 4.7 months (0.39 LYG) with the addition of cetuximab to BSC compared to BSC alone in patients with wild-type KRAS tumours, with a base case of quality adjusted survival of 0.25 QALYs. The PBAC accepted the QALYs as reasonable and this resulted in an ICER of $60,000 cost/QALY.

Therefore, for a patient who achieved a true positive result, the patient had an incremental cost of the treatment of $15,000 (including drug cost and costs of any adverse events for taking the treatment) but also acquired the incremental benefit of 0.25 QALYs over standard treatment. For a patient who has a false negative result, the patient will forgo the cost of treatment, but will also forgo any QALY benefit.

		True mutation status (treatment eligibility)	
		Treatment eligible (Positive)	Treatment ineligible (Negative)
Test result	Positive	True positive	False positive
	Incremental cost *Incremental benefit/loss*	*$15,000* *0.25 QALYs*	*$15,000* *QALYs lost due to toxicity*
	Negative	False negative	True negative
	Incremental costs *Incremental benefit/loss*	*$0* *Potential QALY gains forgone*	*$0* *BSC*

It should be noted, BSC patients will not accrue exactly 0 QALYs (that is, they will live for a period of time with a given quality of life). However, what is important for the *incremental* cost-effectiveness analysis is the magnitude of the costs and QALYs gained or lost as a result of correct versus incorrect treatment allocation. That is, the incremental cost-effectiveness of the sample review will be the same for a given incremental cost and QALY gains for the treatment over BSC irrespective of the absolute magnitude of the costs and QALYs of BSC.

Some tests require the presence of a mutation to rule a patient into treatment (for example, patients positive with the BRAF V600 are eligible for dabrafenib) whereas others require the absence of a mutation for a patient to be allocated to treatment (for example, patients who are KRAS WT are eligible for cetuximab/panitumamb).

This is important because in the instance of determining the absence of a mutation (e.g. KRAS WT) to determine eligibility, it is more likely that a mutation may not be picked in a sub-optimal sample. This means there is a higher chance of obtaining false positive result, i.e. the patient may not be

truly KRAS WT. Consequently, patients will receive treatment that is really not required. Patients incorrectly allocated to PBS treatment will not only accrue the incremental cost of treatment itself but also the costs and quality of life decrements associated with managing toxicities.

On the other hand, in the instance of determining the presence of a mutation to determine eligibility, it is less likely a mutation will be identified in a sub-optimal sample, obtaining a false negative result, where consequently patients will receive not treatment that is needed.

IMPLICATIONS OF DELAYED TESTING

As previously reported, the acceptable maximum turnaround time from ordering of the test, including the time taken to retrieve and review archival tissue where this is applicable (maximum 7 days), to reporting of the test result is 15 working days or 3 weeks. Any test result that is reported after 15 days is considered to be a "test done too late" for the purposes of determining patient treatment management. From the Kaplan–Meier Curve for PFS for WT KRAS patients from Karapetis 2008 (Figure 15), a patient who has not received a test result within 15 days and is waiting potentially for appropriate treatment will follow the BSC care treatment arm. For example, if a patient does not receive a test result for appropriate treatment management for 90 days, then approximately 74% of patient will have progressed, by which time, the treatment option may longer be a viable option as the disease has progressed. Among patients with wild-type KRAS tumours, the PFS was 3.7 months in the cetuximab group and 1.9 months in the BSC group (HR=0.40; 95% CI 0.30 to 0.54, P<0.001) (Figure 15).

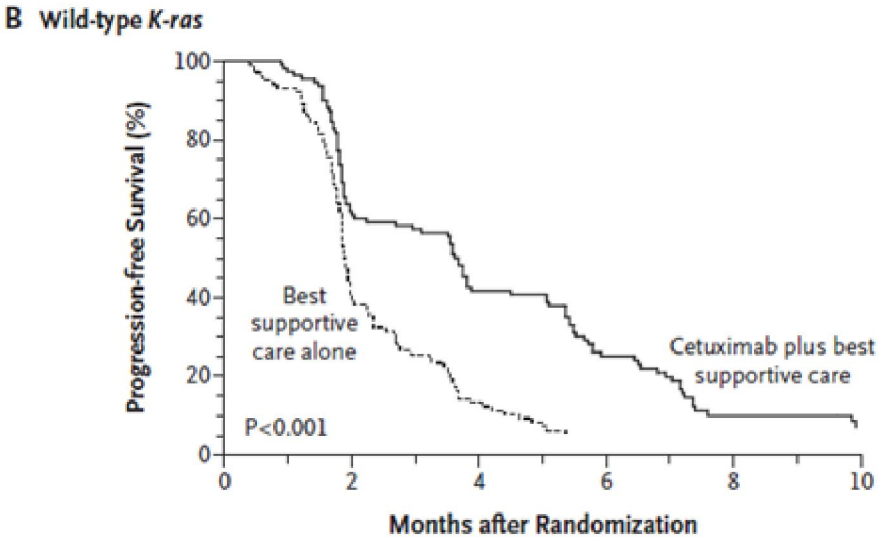

Figure 15 Kaplan–Meier Curves for PFS for WT KRAS patients

Source: Karapetis 2008

COST AND QUALITY OF LIFE IMPACT OF FUTILE TREATMENT

Patients incorrectly allocated to PBS treatment will not only accrue the incremental cost of treatment itself ($15,000 as reported above) but also the costs and quality of life decrements associated with managing toxicities.

The difference in adverse events between patients treated or not treated with cetuximab was 19.4% (Jonker 2007). Rash (11.8% vs. 0.4%), non-neutropenia infection (12.8% vs. 5.5%) and fatigue (33.0% vs. 25.9%) are the main adverse events which were different between the treatment groups. A NICE report on the multiple technology appraisal of cetuximab and panitumumab for the first-line treatment of metastatic colorectal cancer (www.nice.org.uk) reported disutilities of 0.03 for rash (skin reactions) and 0.115 for fatigue (NICE report, Table 75). There was no disutility reported for infection. A simple average of these disutilities is 0.07. Duration of treatment and of AE disutility is the PFS time the of BSC arm because these are patients where treatment is ineffective; 1.9 months (Karapetis 2008). The total QALYs forgone due to toxicities applied in the model is therefore 0.0022 (19.4% of patient * 0.07 disutility * 1.9/12 years). It is acknowledged patients on effective treatment will also accrue these disutilities. However, it is likely these values are already counted within the incremental 0.25 QALYs gained reported above. As such, they are not explicitly added on to patients correctly allocated to treatment. Table 75 of the NICE assessment also reported the costs associated with these AEs; rash (nominal costs, creams are used), fatigue (outpatient visit; MBS item 116); $75.50, Infection (hospitalisation; AR-DRG G60B); $4122. A simple average of these costs is $2098.75. Therefore, total AE costs to applied in the model is $407.16 (0.194 * $2098.75).

SECTION D ECONOMIC EVALUATION

D.1 OVERVIEW

The clinical evaluation in Section B showed turnaround times for archived sample retrieval and review in current practice to be greater than 7 days in over 60% of cases (Scott et al. 2014). The proposed intervention requires this turnaround time to be less than seven days otherwise, the MBS fee is not payable.

Assuming at least some of the laboratories currently taking longer than 7 days will respond to the reimbursement incentive provided by the MBS fee then, the proposed intervention can be considered superior to the main comparator in terms of time taken for an optimal sample to be available for testing. The purpose of the economic model is to quantify the cost and quality of life implications of this improved turnaround time. As such, the form of economic evaluation is cost-utility analysis.

Aside from current practice whereby retrieve and review does take place – albeit with a longer turnaround time than would be the case if MBS funded – the DAP and PASC meeting minutes incorporate a number of other potential comparators:

- Retrieval without review
- No retrieval and patient referred directly for biopsy
- No retrieval, no test, and patient remains ineligible for PBS drug (receives BSC)

Without direct evidence confirming as such, the proposed intervention can nevertheless be assumed to be superior to each one of these comparators on at least one outcome as follows:

- Compared to retrieval without review:
    - Retrieve and review should reduce the number of tests being conducted on sub-optimal tissue which in turn would reduce costs on futile tests and/or improve diagnostic accuracy
- Compared to no retrieval and patient referred directly for biopsy:
    - Retrieve and review has time, cost and quality of life advantages for the patient
- Compared to no retrieval, no test, and patient remains ineligible for PBS drug:
    - Retrieve and review means those patients who would be eligible for the PBS drug go on to receive the efficacy, effectiveness and QALY gains associated with the PBS treatment

As such, cost-utility analysis is also the appropriate form of economic evaluation relative to each of these alternative comparators.

The economic evaluation is a modelled economic evaluation based on the data presented in Section B of this assessment report. The PASC meeting minutes noted “that archiving and retrieval of

pathology samples had already been fully disseminated, and current practice is to archive tissue for at least 10 years". Furthermore, Section B noted that no studies or investigations have ever been made to determine the effectiveness of reviewing the sample prior to testing. As such, essentially all the data in Section B reflects a circumstance where reviewing the sample has occurred – albeit without specific funding for the retrieval and review process.

As described above, the main purpose of the economic model is to quantify the cost and quality of life implications of improved turnaround time (assuming all else remains equal) which should occur if funding for retrieval and review was to be included on the MBS. However, the main difficulty in the economic evaluation of retrieve and review relative to the alternative comparators is not the therapeutic claims of superiority as described above but rather the magnitude of these claims. To this end, the economic model relies on sensitivity analysis and threshold analysis to provide insight in to the extent of superiority required for the proposed retrieve and review MBS item number to be considered cost-effective.

D.2 POPULATIONS AND SETTINGS

As described in Section C.4, the economic evaluation follows a linked evidence approach in order to determine the cost and quality of life implications of delayed or inaccurate test results. These cost and quality of life implications have the potential to vary considerably across the different populations and settings in which archive tissue is reviewed and the corresponding tests undertaken.

As justified in Section C, the economic evaluation focuses on a single population/setting, metastatic colorectal cancer. The structure of the economic model is generic in nature so that it can be used to generate results in other specific indications/circumstances. Sensitivity analyses carried out in Section D.6 can be used to approximate results in the different indications/circumstances.

PATIENT POPULATION

As described and justified above, the patient population in the economic evaluation are patients with metastatic colorectal cancer who are considering treatment with EGFR inhibitors on the PBS.

SETTINGS

The intervention in the economic model is a setting in which a source pathology lab is funded, via the MBS to retrieve and review an archived sample.

The economic model uses four potential comparators (modelled impact relative to funded retrieve and review):

- Unfunded retrieve and review (time delays)
- Retrieval without review (potential for testing on sub-optimal tissues and more test failures/inaccuracies)
- No retrieval and patient referred to biopsy (costs, delays and patient inconvenience)
- No retrieval and patient remains ineligible for PBS drug (forgone health gains)

D.3 STRUCTURE AND RATIONALE OF THE ECONOMIC EVALUATION

A summary of the key characteristics of the modelled economic evaluation is given in Table 30.

Table 30 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
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 EGFR 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 in to the model 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 Number of tests performed 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) are 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

LITERATURE REVIEW

As discussed in Section B, no studies or investigations have ever been made to determine the effectiveness of reviewing the sample prior to testing. Therefore, there are no published economic evaluations of the cost-effectiveness of reviewing the sample.

The structure of the decision analytic economic evaluation is based on the potential alternative settings described above and the linked evidence approach described in Section C.4.

STRUCTURE OF THE ECONOMIC EVALUATION

The premise of the economic model follows the linked evidence approach described in this assessment report and is structured to capture the impact of:

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

The structure of the decision analytic model is presented in Figure 16 to Figure 22

Figure 16 presents the five alternative options considered in the economic model. In the funded and unfunded retrieve and review arms of the model the model first determines the time taken to perform the retrieve and review across the entire cohort (Figure 17). The structure of the model for unfunded retrieve and review is the same as presented in Figure 17. However, the proportion of samples reviewed within one week reflects the funding arrangements (100% when funded, 38% when not funded). As samples pass through each branch of the decision tree the time for the retrieval and review is accumulated (as is the fee for the retrieval process in the funded retrieve and review arm of the model).

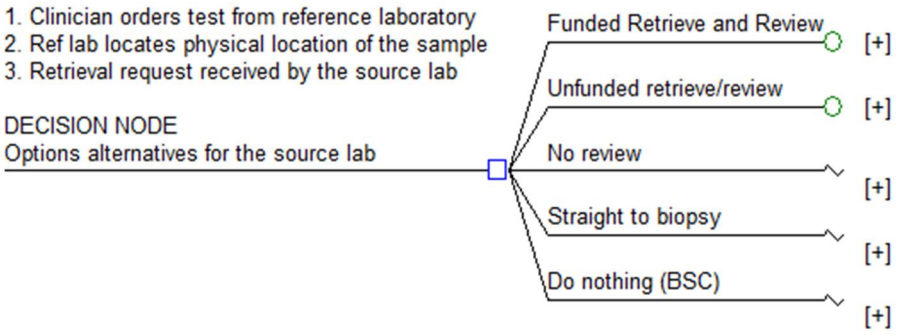

Figure 16 Alternate retrieve and review processes compared in the economic model

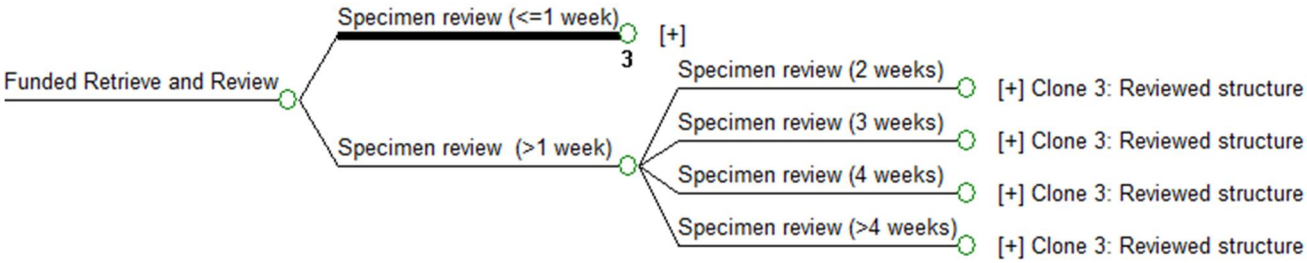

Figure 17 Proportion of samples with various times for sample retrieve and review

Next, the immediate outcome of the review is determined. That is, whether or not suitable archive samples were available for testing (Figure 18). If so, the sample is forwarded for the test to be performed. If not, the patient receives a biopsy and a sample is then forwarded for the test to be performed. As patients require biopsy the time taken, the cost and patient inconvenience (QALY

decrement) are all accumulated. For simplicity, it is assumed all biopsies are successful and provide a sample which will enable an accurate test.

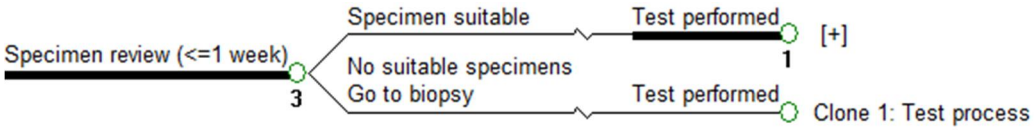

Figure 18 Structure of the model determining the immediate outcome of the sample review

In Figure 19, the immediate outcome of the test is determined. That is, whether or not a test result was obtained with the available sample. The cost of the test is accumulated at this point. If the test is unsuccessful then the patient will be referred for biopsy and then the test performed on the biopsied sample.

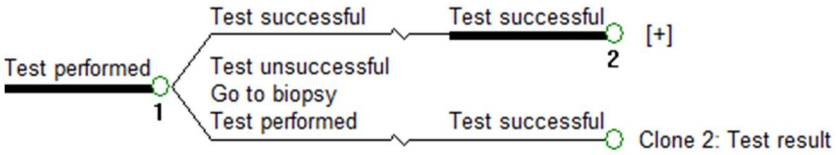

Figure 19 Structure of the model determining the immediate outcome of the sample review

Figure 20 and Figure 21 show how treatment is allocated on the basis of the test results. Firstly, Figure 20 determines if the test result has arrived “on time” or “too late”. The model defines “too late” as a test result which arrives after a patient’s disease has progressed. The probability the test has arrived “too late” probability is a function of the time taken for the test result to reach this point in the decision tree and the time to disease progression whilst on a BSC treatment. For example, if the probability of disease progression at 90 days whilst on BSC is 80% and the test result arrives after 80 days, then the model assumes the patient was exposed to 66 days of progression risk (the 66 days is 14 days less than the 80 days for the test processing time to allow for the fact that the time to disease progression variable is calculated from an optimal and not zero testing time). This 66 days of progression risk means the risk of progression is 73% (66/90) of the 90 day risk and is therefore 59% (73% of 80%). That its, 59% of tests which arrive on day 80 will be considered “too late”. If the test is late the patient does not get treatment and will accrue downstream costs and outcomes associated with BSC. The decision tree then divides these patients in to those who were and were not actually drug indicated. This is for the purposes of assessing true and false negative outcomes in the final node of the decision tree.

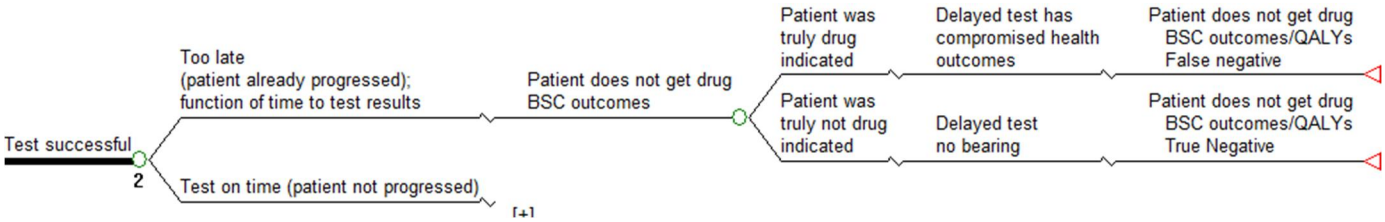

Figure 20 Structure of the decision analytic model for patients where the test result arrives too late (after disease progression)

Figure 21 follows those patients who did receive the test on time (before disease progression). Based on whether the patient was truly drug indicated (or not) the sensitivity (or specificity) variables determine whether the patient will be allocated drug treatment. These sensitivity and specificity variables depend upon whether the test was performed on reviewed, unreviewed or biopsy samples.

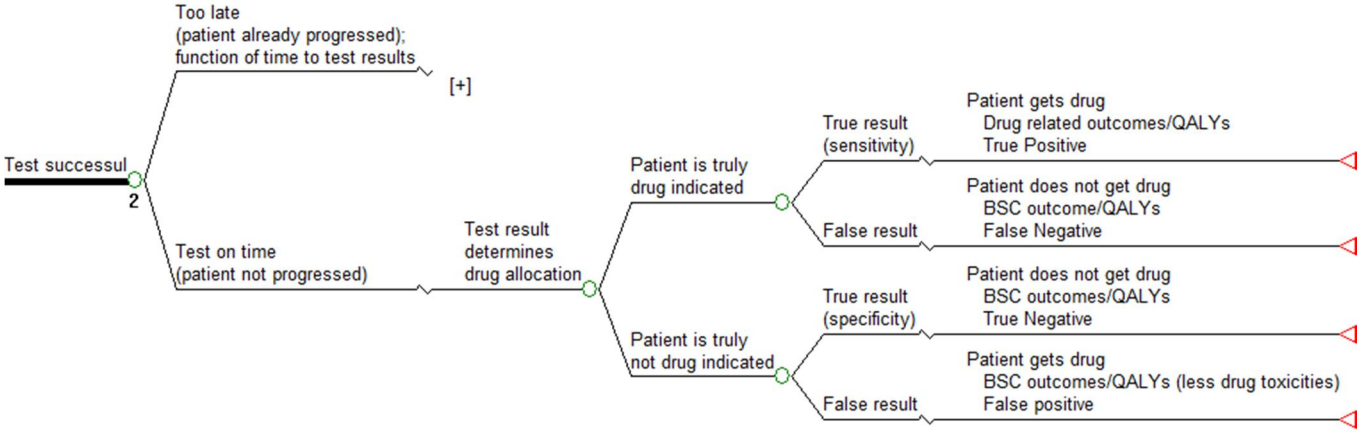

Figure 21 Structure of the decision analytic model for patients where the test result arrives on time (before disease progression)

Figure 22 presents the structure of the model for the no review, straight to biopsy and no testing arms. The patients in these arms of the model go straight to a test without review, to a test via biopsy or receive no test at all. The structure of the model from the point of the test remains the same although the test failure rates and accuracy will depend upon the typo of sample the test is performed on. In the case of “no testing”, this is the same as a test where all patients are considered negative for drug treatment (0% sensitivity because no “positive” patients go on to be treated, 100% specificity because no “negative” patients go on to be treated). The cost of testing is not accrued in this arm of the model.

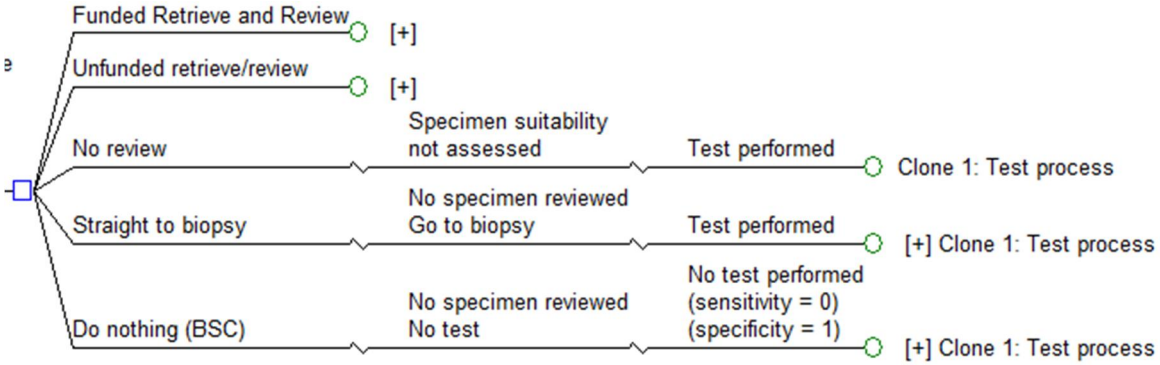

Figure 22 Structure of the model for the no review, straight to biopsy and no testing arms

ASSUMPTIONS INCORPORATED INTO THE MODEL STRUCTURE:

The assumptions of the economic model can be inferred from the description of the model structure itself. Some of the key implicit assumptions to consider are as follows:

- The only difference between the funded and unfunded arms of the model is the time taken to receive a sample ready for testing. It is assumed the results obtained from the sample are the same from this point on in the model (because all samples have been reviewed). Implicit in this assumption is the fact the clinician will continue to wait for the sample and not refer the patient for biopsy in the interim.
- When patients have a failed test result, they will be referred for biopsy. Biopsy is always successful at obtaining an accurate test result. The model does not explicitly incorporate complications associated with biopsy. These assumptions are likely biased against retrieve and review because it minimises the possible consequences of a failed test result.
- If patients experience disease progression whilst waiting test results they will no longer be eligible for treatment irrespective of their test outcome. This was a necessary simplifying assumption which likely favours funded retrieve and review because it implies a strictly applied consequence of not receiving a test result on time.
- The model duration is not explicitly specified. Rather, long term cost and outcomes are based on the incremental long term cost and outcomes of treatment itself. It is these long term cost and outcomes which are influenced by correct decision-making in the short term.

D.4 INPUTS TO THE ECONOMIC EVALUATION

The inputs in to the modelled economic evaluation are presented in the following categories:

- Cost variables
- Quality of life variables
- Retrieve, review and test turnaround times
- Sample suitability variables

- Test accuracy variables
- Downstream metastatic colorectal cancer (mCRC) specific variables

COST VARIABLES

The main cost variables (not including downstream treatment costs which are described later) included in the economic model are the costs of:

- the retrieve and review process (applied only to the arm of the model where this process is funded by the MBS)
- the cost of the molecular test
- the cost of any biopsies required

The costs used in the economic model and the source of these cost estimates is summarised in Table 31.

Table 31 Cost items included in the economic evaluation

Cost item	Cost	Reference
Archive retrieve and review	$150	Proposed fee
Molecular test	$362.59	MBS item 73338
Biopsy	$1632	AR-DRG V7.0, Round 18 (2013-14) Sameday colonoscopy, G48C

QUALITY OF LIFE VARIABLES

Most of the quality of life variables in the economic model relate to the downstream consequences of treatment and are presented with the other consequences of this downstream treatment in a sub-Section to follow. However, the process of undergoing a biopsy is assumed to have a quantifiable impact on the patient's quality of life.

In a cost-effectiveness analysis of colonoscopic surveillance conducted by NICE the discomfort of undergoing a colonoscopy was estimated to be associated with a decrement of 0.0025 QALYs. This discomfort comprises the disability caused by bowel preparation and the recovery period after the procedure. The value of 0.0025 is used in Saini et al. (2010) assuming a 2-day event which halves the patient's procedure free utility value weight of 0.91 (0.0025 = 0.91 / 2 × 2 / 365).

No other complications associated with biopsies are included in the economic evaluation.

RETRIEVE, REVIEW AND TEST TURNAROUND TIMES

RETRIEVE AND REVIEW TIMES

The retrieve, review and test turnaround times are based on the study by Scott (2014) presented in Section B (see Figure 23).

Table 32 presents the data as they applied in the economic model.

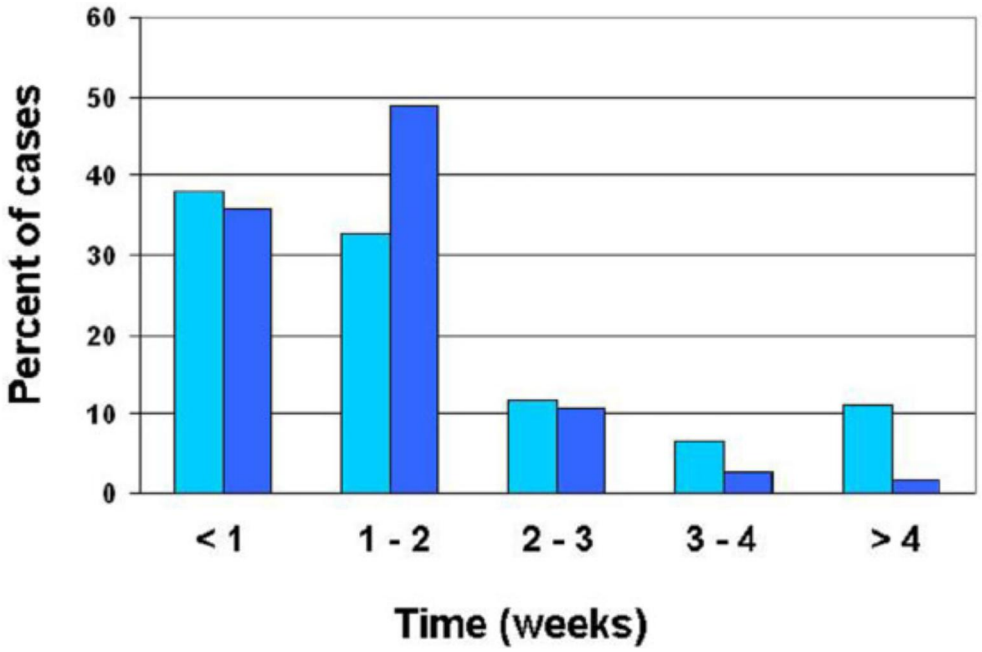

Figure 23 **Time elapsed between ordering of the KRAS test and reception of the sample in the test laboratory (light shading), and between reception of the sample and reporting of the KRAS mutation test result (dark shading).**

Source: Reproduction of Figure 1, Scott et al. (2014)

Table 32 **Retrieve and review turnaround times applied in the economic model in the current practice arm of the model (where the process is unfunded)**

Retrieve and review time	Percent of cases	Source	Time applied in the model (days)
< 1 week	38%	Figure 1 of Scott et al. 2014 (see Figure 23)	7
1 to 2 weeks	33%		14
2 to 3 weeks	11%		21
3 to 4 weeks	7%		28
> 4 weeks	11%		50 (Assumption)

As discussed in Section B, the extent to which MBS funding of retrieve and review will change the behaviour of pathology labs and therefore the extent to which turnaround times will be improved has not been investigated in the literature. For the purposes of defining a base case in the economic evaluation it will be assumed **all** of the 62% of retrieve and review processes that are not currently taking place within 7 days will do so in the arm of the model where MBS funding is provided. This assumption favours the funded retrieve and review arm of the model. This is likely to be an important assumption in the economic model because the proposed MBS item fee will mean the MBS will be paying for a service that is already conducted in 38% of cases. The extent to which the proposed funding will be cost-effective (from the perspective of the MBS) will depend upon the amount of services in the remaining 62% which will move to within the seven-day period and the benefit this timeliness confers to patients. The proportion of retrieve and review process which will move from >7 days to within 7 days will be tested in sensitivity analysis.

TEST TURNAROUND TIMES

Once the retrieve and review process has been completed and the time taken recorded, the time taken to complete the test is accumulated. This time is assumed to be constant for all samples irrespective of time taken for the review process. Based on Scott et al. (2014) where more than 85% of tests were completed within 2 weeks (see Figure 23 above) it is assumed in the model the test turnaround time will be 7 days. This is tested in sensitivity analysis.

BIOPSY TURNAROUND TIMES

When patients are referred for biopsy in the model (either as a comparator option, after a test result has failed, or when a suitable archive sample cannot be identified) the model will accumulate the time taken to undertake the biopsy and prepare the sample for testing/analysis.

A suitable time for biopsy in mCRC could not be identified in the literature. Shaaban (2013) investigated 115 consecutive cases of core biopsy and excision HER2 testing for breast cancer. In this study the mean time from decision to refer for biopsy to receipt of final results was 17 days. Given the model has allocated 7 days for the test turnaround time (see above), the time for the biopsy process in the model is 10 days. This value is tested in sensitivity analysis.

SAMPLE SUITABILITY VARIABLES

As in Section B, the model uses two variables to assess the suitability of the sample as it proceeds through the retrieve and review process: “No test” and “Test without result”.

- “No test” is where archive tissue is unavailable for testing because, upon review, it is considered sub-optimal for testing due to, for example, insufficient tissue quality or quantity. The significance of this measure is it provides an indication of the proportion of futile tests avoided because of the archival tissue review process. That is, in a world where “no review” takes place, these samples would be forward directly for testing and the MBS fee for the test will be accrued without providing a test result (This is considered a hypothetical scenario in that it is unlikely an MBS fee would actually be charged for a test that cannot be performed. However, it is indicative of a scenario where literally “no review” of the sample has taken place).
- “Test without result” is where, on review, an archival tissue sample has been deemed suitable for testing, however, on subsequent analysis the sample has failed to yield an interpretable result, for example due to there being an insufficient quantity of extractable DNA or the DNA being degraded. The significance of this measure is it provides an indication of the proportion of futile tests which cannot be avoided because of the archival tissue review process and where biopsy might be considered.

The “No Test” value ranged from 5 to 10% across a range of studies presented in Section B. The economic model uses a value of 5.3% based on the study by Lievre (2013) presented in Section B. This value is applied to the circumstance where a review has taken place (irrespective of the time

taken to undertake that review).

The "Test without result" generally remained below 5% in the studies presented in Section B. The economic model uses a weighted average of the three main studies of KRAS testing for mCRC presented in Section B: in Bibeau (2010), 15 out of 575 samples did not yield a test result; in the European cohort of Cierdiello (2011) test results were unobtainable in 70 of 1679 samples; and in Chretien (2013) this figure was 10 of 674 (See Section B for more information). Therefore the economic model uses a test without result probability of 3.2% [(15+70+10)/(575+1679+674)]

Taken together, the model estimates for a world where reviews do take place, 8.3% of cases will not yield a test result from archived tissue and biopsy will be required (5.3% where no suitable archive tissue is available for testing + 3.2% of the remaining 94.7% where the test does not yield a usable result). In a world where no review takes place, these 8.3% of cases will be directed straight to the test, the cost of the test will be accrued and a biopsy will be required because there will be no usable test result.

The extent to which this variable would be altered should no review be undertaken is hypothetical and tested in sensitivity analysis. For the purposes of describing a base case analysis it is assumed the review process decreases the 8.3% figure by 5%. That is, 13.3% of cases will not yield a test result in the no review arm of the model.

TEST ACCURACY VARIABLES

The extent to which an unreviewed sample could or would compromise test accuracy is again a hypothetical value tested in sensitivity analysis of the model. As described in Section B, reviewing archive samples is established practice and there is no evidence comparing results of reviewed and unreviewed samples.

For the purposes of describing a base case analysis, it is assumed tests done on reviewed archive tissue or when the patient undergoes biopsy are completely accurate. That is, 100% sensitive and 100% specific. This is considered a reasonable assumption given that the evidence of patient outcomes linked to this diagnostic accuracy is based on treatment allocations where samples were reviewed. That is, even though the allocation to treatment may not be completely consistent with the underlying "truth" of the patient's status, any error in this allocation is implicit within the outcomes of treatment that flow from this allocation.

The economic model describes sensitivity and specificity in relation to the patient's eligibility for PBS subsidised treatment. That is, a positive result means the patient is eligible for treatment. It should be noted that some tests require the presence of a mutation to rule a patient in to treatment (eg: BRAF inhibitors for melanoma) whereas others require the absence of a mutation for a patient to be allocated to treatment (eg: KRAS for EGFR inhibitors). Discussion with the applicants during the preparation of this assessment report indicated that, whilst both inaccurate results (false positive and false negative) are theoretically possible due to a failure to review, it is likely that a failure to review is more likely to be associated with a failure to identify/detect a mutation.

In the base case economic evaluation, which is based on mCRC, a failure to detect a mutation means patients will be erroneously allocated to PBS treatment. In the specification used in the economic model where allocation to PBS treatment means "positive", this is a false positive result and the specificity of the test result is therefore less than 100%. For the purposes of establishing a base case analysis a specificity for unreviewed samples of 95% is used. The sensitivity of unreviewed samples is 100%. Both these values are tested in sensitivity analysis. Importantly, a sensitivity analysis of the sensitivity value will be useful in examining the impact of potential errors in allocating treatments, like BRAF inhibitors for melanoma, where a failure to identify a mutation means patients will forgo effective treatments.

DOWNSTREAM MCRC SPECIFIC VARIABLES

Once patients have been allocated to treatment (or not) based on the results of their test the model then captures the impact of their treatment allocation on long term costs and outcomes. These variables were described and justified in Section C.4. For convenience, Table 33 summarises the variables used to populate the downstream cost outcomes of the model.

Table 33 Downstream costs and outcomes of treatment allocation used in the model

Model variable	Value	Reference and Notes
Proportion of patients with disease progression by 90 days; BSC	0.74	Karapetis (2008). See Section C.4 This variable is used to determine if the test result has arrived too late. Patients who progress before the test result has arrived will not receive PBS treatment (irrespective of the test result)
Prevalence of patients who should be allocated to drug treatment (i.e. free of KRAS mutation)	37.5%	Page 11 of the DAP
Incremental cost of PBS drug treatment for those indicated	$15,000	PBAC PSDs Only the incremental costs and QALY gains (relative to standard of care) are included in the model. These represent the incremental effect of the test result and are all that is necessary for accurate calculation of the ICERs
Incremental QALYS gained with PBS drug treatment for those indicated	0.25	
Cost of drug toxicities accumulated by patients who are misallocated to drug treatment	$407.16	Section C.4 Only patients incorrectly receiving drug treatment accrue these costs. These costs are implicit in the incremental cost of drug treatment in patients being correctly treated
QALY impact of drug toxicities accumulated by patients who are misallocated to drug treatment	-0.0022	

D.5 RESULTS OF THE ECONOMIC EVALUATION

DISAGGREGATED COSTS

Disaggregated cost estimates are summarised in Table 34 for each of the five alternatives in the model.

The cost of biopsies and tests for both the funded and unfunded retrieve and review arms of the model ($136 and $374, respectively) was lower compared to the cost of biopsies and tests for the

retrieval without review arm ($218 and $411, respectively). This is due to less sub-optimal tissues samples progressing to diagnostic testing from the review process, and a request for a re-biopsy and another diagnostic test is less likely when a review of the sample has been conducted.

There was a cost associated with futile treatment in the no review arm (but not in any of the other arms of the model). This is because test results conducted on unreviewed samples are assumed to have less than 100% specificity. That is, because the sample had not been reviewed, there was a higher chance of incorrect determination of eligibility of PBS treatment, and therefore incorrect treatment allocation.

Overall the total cost was highest in the straight to biopsy arm ($7,481). The difference between the total overall costs between funded and unfunded treatment review was the cost of the proposed service, $150, which was only applied to the funded retrieve and review scenario and the cost of effective treatment.

Compared to unfunded retrieve and review the proposed funding of retrieve and review had incremental costs of $615 per patient ($6,236-$5,621). This incremental cost is higher than the proposed fee itself ($150) because more patients are being allocated to PBS funded treatment.

Table 34 Disaggregated cost estimates

Cost item	Funded Retrieve / Review	Unfunded Retrieve / Review	Retrieval without review	Straight to biopsy	Do not test
Retrieve/Review	$150.00	$0.00	$0.00	$0.00	$0.00
Biopsies	$135.95	$135.95	$217.55	$1,632.00	$0.00
Tests	$373.58	$373.58	$410.92	$362.59	$0.00
Treatment (effective)	$5,576.66	$5,111.85	$5,557.18	$5,486.25	$0.00
Treatment (futile)	$0.00	$0.00	$417.29	$0.00	$0.00
Total	$6,236.19	$5,621.38	$6,602.95	$7,480.84	$0.00

DISAGGREGATED OUTCOMES

Disaggregated health outcome estimates are summarised in Table 34 for each of the five scenarios in the model. On average, although the time to final test result was the shortest in the retrieval without review scenario (10 days), 2.7% of patient would obtain a false positive result. Also, 13.3% of patients would still require a re-biopsy for testing on a new sample. Unfunded retrieval and review had the longest time to final test result (25 days) and consequently, 3.4% of patients obtained a false negative result. This includes patients who received “treatment too late”, which as a function of the delayed time to final test result, had been on inadequate treatment, mostly likely allocated to BSC.

Across the five scenarios, the highest number of true positives (37.2%) and true negatives (62.5%), resulted from the funded retrieve and review scenario. The risk of obtaining a false negative result was very low (0.3%). Additionally, receiving a test result too late was lower (0.9%) compared to unfunded retrieve and review (9.1%). Furthermore, the funded retrieve and review scenario resulted in the greatest QALYs compared to BSC; 0.0927 QALYs.

Table 35 Disaggregated health outcome estimates

Outcome	Funded Retrieve / Review	Unfunded Retrieve / Review	Retrieval without review	Straight to biopsy	Do not test
Time to final test result (days)	15.05	25.10	10.27	17.00	0.00
Number of tests performed (per patient)	1.0303	1.0303	1.1333	1.0000	0.0000
Test result too late (% of patients)	0.9%	9.1%	1.2%	2.5%	0.0%
Biopsies required (% of patients)	8.3%	8.3%	13.3%	100.0%	0.0%
Accuracy of treatment allocation (% of patients)					
True positive	37.2%	34.1%	37.0%	36.6%	0.0%
False negative	0.3%	3.4%	0.5%	0.9%	37.5%
False positive	0.0%	0.0%	2.7%	0.0%	0.0%
True negative	62.5%	62.5%	59.8%	62.5%	62.5%
Total QALYs (incremental to BSC)	0.0927	0.0850	0.0922	0.0889	0.0000
impact of biopsies	-0.0002	-0.0002	-0.0003	-0.0025	0.0000
impact of futile tx	0.0000	0.0000	-0.0001	0.0000	0.0000

INCREMENTAL COST-EFFECTIVENESS

The incremental costs and outcomes as calculated for the proposed retrieve and review service relative to each of the alternative comparators are presented in Table 36.

Funded retrieve and review dominates retrieve without review and biopsy, due to higher costs from additional tests, biopsies and inappropriate treatment allocation based on a futile 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.

Table 36 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

The results of the model are presented on the cost-effectiveness plane in Figure 24. Figure 24 illustrates the higher costs and worse outcomes of the straight to biopsy and no review alternatives. The relatively straight line from BSC, through current practice (i.e. unfunded review) to the proposed funded retrieve and review alternative suggests the proposed funding has a similar level cost-effectiveness compared to current practice as current practice has relative to doing nothing. This likely reflects the fact the cost-effectiveness of improving the outcomes of testing depends heavily on the cost-effectiveness of drug treatment.

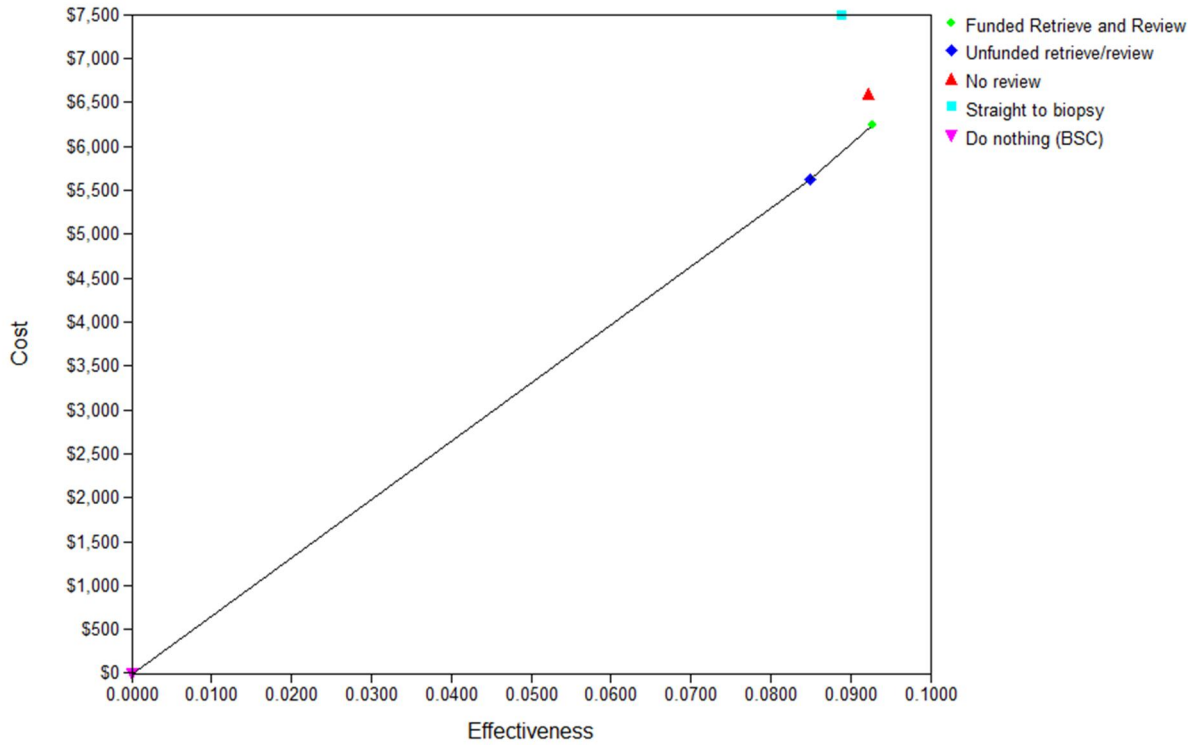

Figure 24 Results of the economic model on the cost-effectiveness plane

ALTERNATIVE BASE CASE SCENARIOS

Due to the fact review of samples is widely disseminated in to clinical practice it was not possible to quantify the superiority of funded retrieve and review. As such, the model used hypothetical values the impact of which are explored here.

FUNDED VERSUS UNFUNDED RETRIEVE AND REVIEW

In this comparison there was one hypothetical advantage for funded retrieve and review, that being the proportion of cases currently taking greater than 7 days which will respond to the funding incentive. The base case was 100%. As this proportion decreases the incremental cost-effectiveness ratio increases – although it is not until a response rate of less than 30% does the ICER reach $100,000 and begin to increase quite dramatically (Figure 25).

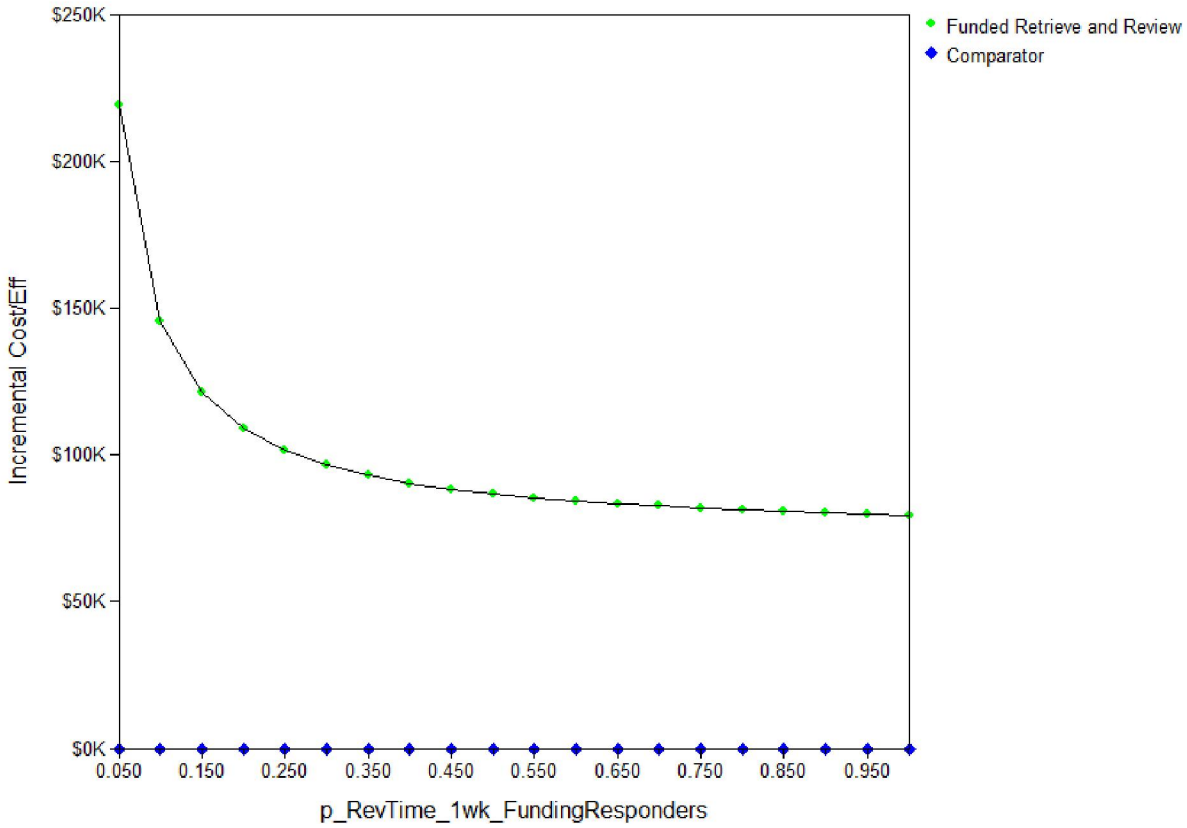

Figure 25 Result of the model for various levels of response to the funding incentive

FUNDED RETRIEVE AND REVIEW VERSUS NO REVIEW

In this comparison there were two hypothetical advantages of funded retrieve and review: 5% fewer test failures (8.3% versus 13.3%) and better specificity (100% versus 95%) for allocation to drug treatment. It is also possible for retrieve review to have better sensitivity. The impact of each of these three variables on the cost-effectiveness ratio are presented multiway sensitivity analyses in Table 37, Table 38 and Table 39.

Table 37 shows funded retrieve and review remains dominant (i.e. cost-saving with improved health outcomes) with or without advantages in test failure rates while ever the review process conferred a specificity advantage. This is because the improved specificity of the review process means patients are not inappropriately exposed to costly treatment on the PBS. When there is no advantage in specificity or sensitivity, the funded retrieve and review arm of the model needs to avoid between 6 and 7% of failed tests in order to reach an incremental cost per QALY ratio of approximately $50,000.

Table 37 Impact of test failures avoided with the reviewing process on the incremental cost-effectiveness ratio of funded review versus no review – under alternative conditions of sensitivity and specificity superiority claims

Test failures avoided with reviewed samples (versus unreviewed samples)	Specificity and Sensitivity of unreviewed samples (1 and 1 for reviewed samples)			
	Spec 1; Sens 1	Spec 1; Sens 0.95	Spec 0.95; Sens 1	Spec 0.95; Sens 0.95
0	Dominated	91,156	8,725,170	DOMINANT
0.01	10,482,957	85,662	DOMINANT	DOMINANT
0.02	790,707	80,328	DOMINANT	DOMINANT
0.03	348,798	75,148	DOMINANT	DOMINANT
0.04	192,403	70,114	DOMINANT	DOMINANT
0.05	112,380	65,220	**DOMINANT**	DOMINANT
0.06	63,767	60,461	DOMINANT	DOMINANT
0.07	31,104	55,831	DOMINANT	DOMINANT
0.08	7,647	51,324	DOMINANT	DOMINANT
0.09	DOMINANT	46,937	DOMINANT	DOMINANT
0.1	DOMINANT	42,665	DOMINANT	DOMINANT

Shaded cell represents the base case analysis presented above

Table 38 shows funded retrieve and review has a favourable (or cost-saving) incremental cost-effectiveness ratio whenever specificity without review is worse than 97.5% (irrespective of assumptions about sensitivity or test failure rates). As described above, this can be explained by the avoidance of high cost, ineffective treatment with false positive outcomes.

Table 38 Impact of superior specificity with the reviewing process on the incremental cost-effectiveness ratio of funded review versus no review – under alternative conditions of test failure and sensitivity claims

Specificity of test results on unreviewed samples	Test failure and Sensitivity of unreviewed samples (0 and 1 for reviewed samples)			
	Test Fail 0; Sens 1	Test Fail 0.05; Sens 1	Test Fail 0; Sens 0.95	Test Fail 0.05; Sens 0.95
0.8	DOMINANT	DOMINANT	DOMINANT	DOMINANT
0.825	DOMINANT	DOMINANT	DOMINANT	DOMINANT
0.85	DOMINANT	DOMINANT	DOMINANT	DOMINANT
0.875	DOMINANT	DOMINANT	DOMINANT	DOMINANT
0.9	DOMINANT	DOMINANT	DOMINANT	DOMINANT
0.925	112,696,239*	DOMINANT	DOMINANT	DOMINANT
0.95	8,725,170*	**DOMINANT**	DOMINANT	DOMINANT
0.975	1,414,042*	DOMINANT	38,296	18,856
1	Dominated	112,380	91,156	65,220

Shaded cell represents the base case analysis presented above.
* These ICERs represent a scenario where funded retrieve and review results in less costs and less QALYs compared to no review. The fact these ICERs are very high means a high amount of costs are saved for a small QALY forgone.

Table 39 shows the impact of improved specificity with funded retrieve and review is less pronounced when considered with improved sensitivity. This is because the drug costs savings from fewer false positives are offset by increased costs in true positives. This, however, also contributes to QALY gains meaning the overall benefit of retrieve and review (relative to no review) in these scenarios is the QALY gains conferred to patients who would not get treated if the sample is not reviewed. This means the cost-effectiveness of retrieve and review depends heavily on the cost-effectiveness of drug treatment.

Table 39 Impact of superior sensitivity with the reviewing process on the incremental cost-effectiveness ratio of funded review versus no review – under alternative conditions of test failure and specificity claims

Sensitivity of test results on unreviewed samples	Test failure and Specificity of unreviewed samples (0 and 1 for reviewed samples)			
	Test Fail 0; Spec 1	Test Fail 0.05; Spec 1	Test Fail 0; Spec 0.95	Test Fail 0.05; Spec 0.95
0.8	67,653	61,410	41,672	36,294
0.825	68,754	61,606	39,047	33,024
0.85	70,224	61,864	35,545	28,708
0.875	72,288	62,221	30,637	22,749
0.9	75,396	62,747	23,266	13,985
0.925	80,608	63,599	10,951	DOMINANT
0.95	91,156	65,220	DOMINANT	DOMINANT
0.975	123,821	69,494	DOMINANT	DOMINANT
1	Dominated	112,380	8,725,170	**DOMINANT**

Shaded cell represents the base case analysis presented above.

STEPPED ECONOMIC EVALUATION

Given the disparate, non-trial-based, nature of the evidence supporting the economic model a stepped economic evaluation is not presented. The detailed disaggregated results presented above and to follow in the sensitivity analysis below provide insight in to how the different features of retrieve and review process (time to test result, test failure rates, accuracy of test result) translate to patient costs, outcomes and QALYs.

D.6 SENSITIVITY ANALYSES

Sensitivity analyses of the economic model were conducted for a range of variables and for each of the comparators (Table 40).

The main drivers of the cost-effectiveness of funded retrieve 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 retrieve and review remained dominant compared to either no review or to biopsy across a range of scenarios tested. This is due to higher costs associated with receiving misallocated

treatment (the base case model assumed more false positive allocation to treatment when samples are note reviewed), and higher costs associated with biopsy, respectively.

The main drivers of the cost-effectiveness of funded retrieve 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 retrieve 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.

Table 40 Sensitivity analyses

Variable	Base case value	Sensitivity analysis value	Incremental cost per QALY of Funded retrieve and review versus…..			
			Unfunded R/R	No R/R	Biopsy	No test
Base case	-	-	**$79,363**	**Dominant**	**Dominant**	**$67,247**
Cost variables						
Cost of the proposed service	$150	$0	$60,000	Dominant	Dominant	$65,629
		$50	$66,454	Dominant	Dominant	$66,168
		$100	$72,908	Dominant	Dominant	$66,247
Cost of the test	$362.59	$200	$79,363	Dominant	Dominant	$65,440
		$250	$79,363	Dominant	Dominant	$65,996
		$300	$79,363	Dominant	Dominant	$66,551
		$350	$79,363	Dominant	Dominant	$67,107
		$400	$79,363	Dominant	Dominant	$67,662
Cost of biopsy	$1,632	$0	$79,363	Dominant	Dominant	$65,781
		$500	$79,363	Dominant	Dominant	$66,230
		$1,000	$79,363	Dominant	Dominant	$66,679
		$1,500	$79,363	Dominant	Dominant	$67,128
		$2,000	$79,363	Dominant	Dominant	$67,577
Quality of life variables						
QALY impact of biopsy	-0.0025	0.000	$79,363	Dominant	Dominant	$67,096
		-0.005	$79,363	Dominant	Dominant	$66,797
		-0.010	$79,363	Dominant	Dominant	$66,500
		-0.015	$79,363	Dominant	Dominant	$66,206
		-0.020	$79,363	Dominant	Dominant	$65,914
Retrieve, review and test turnaround times						
Retrieve and review times: Proportion of samples returned within 1 week when funded (vs 38% when unfunded)	100%	40%	$300,097	NoRR v FRR*: $129,738	Biopsy v FRR*: $482,499	$66,828
		60%	$92,740	NoRR v FRR*: $161,880	Biopsy v FRR*: $1,337,782	$66,976
		80%	$82,866	NoRR v FRR*:	Dominant	$67,115

Variable	Base case value	Sensitivity analysis value	Incremental cost per QALY of Funded retrieve and review versus…..			
			Unfunded R/R	No R/R	Biopsy	No test
Base case	-	-	**$79,363**	**Dominant**	**Dominant**	**$67,247**
				$274,757		
Retrieve and review times: Proportion of samples returned within 1 week when unfunded (vs 100% when funded)	38%	20%	$75,006	Dominant	Dominant	$67,247
		40%	$80,008	Dominant	Dominant	$67,247
		60%	$90,012	Dominant	Dominant	$67,247
		80%	$120,024	Dominant	Dominant	$67,247
Test turnaround time: Days from sample to test result (all scenarios)	7	0	$92,050	Dominant	Dominant	$67,199
		5	$81,832	Dominant	Dominant	$67,233
		10	$79,363	Dominant	Dominant	$67,438
		15	$79,363	Dominant	Dominant	$67,780
		20	$79,363	Dominant	Dominant	$68,155
Biopsy turnaround time: Time from ordering biopsy to sample ready for testing	10	0	$79,363	Dominant	Dominant	$67,197
		5	$79,363	Dominant	Dominant	$67,222
		10	$79,363	Dominant	Dominant	$67,247
		15	$79,363	Dominant	Dominant	$67,272
		20	$79,363	Dominant	Dominant	$67,297
Sample suitability variables						
Additional test failures when sample not reviewed	5%	1%	$79,363	Dominant	Dominant	$67,247
		10%	$79,363	Dominant	Dominant	$67,247
		15%	$79,363	Dominant	Dominant	$67,247
		20%	$79,363	Dominant	Dominant	$67,247
		25%	$79,363	Dominant	Dominant	$67,247
Test accuracy variables						
Sensitivity and specificity of unreviewed samples (reviewed samples always 100% by definition)	100% and 95%	100% and 100%	$79,363	$112,295	Dominant	$67,247
		100% and 95%	$79,363	Dominant	Dominant	$67,247
		100% and 90%	$79,363	Dominant	Dominant	$67,247
		100% and 85%	$79,363	Dominant	Dominant	$67,247
		100% and 80%	$79,363	Dominant	Dominant	$67,247

Variable	Base case value	Sensitivity analysis value	Incremental cost per QALY of Funded retrieve and review versus…..			
			Unfunded R/R	No R/R	Biopsy	No test
Base case	-	-	**$79,363**	**Dominant**	**Dominant**	**$67,247**
		95% and 100%	$79,363	$65,224	Dominant	$67,247
		95% and 95%	$79,363	Dominant	Dominant	$67,247
		95% and 90%	$79,363	Dominant	Dominant	$67,247
		95% and 85%	$79,363	Dominant	Dominant	$67,247
		95% and 80%	$79,363	Dominant	Dominant	$67,247
		90% and 100%	$79,363	$62,746	Dominant	$67,247
		90% and 95%	$79,363	$13,986	Dominant	$67,247
		90% and 90%	$79,363	Dominant	Dominant	$67,247
		90% and 85%	$79,363	Dominant	Dominant	$67,247
		90% and 80%	$79,363	Dominant	Dominant	$67,247
		85% and 100%	$79,363	$61,866	Dominant	$67,247
		85% and 95%	$79,363	$28,708	Dominant	$67,247
		85% and 90%	$79,363	Dominant	Dominant	$67,247
		85% and 85%	$79,363	Dominant	Dominant	$67,247
		85% and 80%	$79,363	Dominant	Dominant	$67,247
		80% and 100%	$79,363	$61,411	Dominant	$67,247
		80% and 95%	$79,363	$36,293	Dominant	$67,247
		80% and 90%	$79,363	$11,355	Dominant	$67,247
		80% and 85%	$79,363	Dominant	Dominant	$67,247
		80% and 80%	$79,363	Dominant	Dominant	$67,247
Downstream treatment specific variables						
Prevalence of patients to be allocated to treatment	0.375	0.25	$89,044	Dominant	Dominant	$70,882
		0.50	$74,522	Dominant	Dominant	$65,432
		0.75	$69,681	Dominant	Dominant	$63,619
Proportion with disease progression at 90 days	0.74	0.20	$131,642	Dominant	Dominant	$67,201
		0.40	$95,821	Dominant	Dominant	$67,218
		0.60	$83,881	Dominant	Dominant	$67,235

Variable	Base case value	Sensitivity analysis value	Incremental cost per QALY of Funded retrieve and review versus…..			
			Unfunded R/R	No R/R	Biopsy	No test
Base case	-	-	**$79,363**	**Dominant**	**Dominant**	**$67,247**
		0.80	$77,910	Dominant	Dominant	$67,252
		1.00	$74,328	Dominant	Dominant	$67,269
Incremental cost of PBS drug treatment for those indicated	15000 (ICER of $60,000)	$5000 ($20,000)	$39,363	Dominant	Dominant	$27,157
		$10000 ($40,000)	$59,363	Dominant	Dominant	$47,202
		$15000 ($60,000)	$79,363	Dominant	Dominant	$67,247
		$20000 ($80,000)	$99,363	Dominant	Dominant	$87,292
Incremental QALYS gained with PBS drug treatment for those indicated	0.25 (ICER of $60,000)	0.10 ($150,000)	$198,407	Dominant	Dominant	$168,685
		0.50 ($30,000)	$39,681	Dominant	Dominant	$33,586
		0.75 ($20,000)	$26,454	Dominant	Dominant	$22,382
		1.00 ($15,000)	$19,841	Dominant	Dominant	$16,783
Cost of drug toxicities accumulated by patients who are misallocated to drug treatment	407.16	0	$79,363	Dominant	Dominant	$67,247
		500	$79,363	Dominant	Dominant	$67,247
		1000	$79,363	Dominant	Dominant	$67,247
		1500	$79,363	Dominant	Dominant	$67,247
		2000	$79,363	Dominant	Dominant	$67,247
QALY impact of drug toxicities accumulated by patients who are misallocated to drug treatment	-0.0022	0.000	$79,363	Dominant	Dominant	$67,247
		-0.005	$79,363	Dominant	Dominant	$67,247
		-0.010	$79,363	Dominant	Dominant	$67,247
		-0.015	$79,363	Dominant	Dominant	$67,247
		-0.020	$79,363	Dominant	Dominant	$67,247
		-0.025	$79,363	Dominant	Dominant	$67,247
		-0.030	$79,363	Dominant	Dominant	$67,247

* These results reflect a cost-effectiveness ratio whereby the proposed intervention (funded retrieve and review) is both less costly and has less QALYs than the comparator. The ratios therefore reflect the cost savings for every QALY forgone in the given sensitivity analysis. Higher ratios reflect higher cost savings could be made for every QALY forgone, and therefore suggest improving cost-effectiveness of the proposed intervention. In these scenarios no review can result in more QALYs than funded retrieve and review because no review is faster than funded review and the QALYs from this timeliness are greater than the QALYs lost due to potential inaccuracies.

The results of each of the sensitivity analyses in Table 40 are explained as follows.

Funded retrieve and review nearly always remained dominant compared to biopsy. This is because biopsy is more costly than the proposed service and has potential safety implications for the patient. In certain circumstances, when the proportion of samples delivered within one week was very low, biopsy had better outcomes than funded retrieve and review. This is because biopsy was more timely than funded retrieve and review. However, these better outcomes with biopsy came at very high cost (upwards of $400,000 per QALY gained) and suggests funded retrieve and review remained cost-effective relative to biopsy.

Similarly, funded retrieve and review nearly always remained dominant compared to no review. This is because the model assumed no review was associated with false positive allocation to expensive treatment. When this assumption is relaxed, the incremental cost per QALY of funded retrieve and review remained better than $70,000 except when no review is assumed to be equally accurate as funded review (ICER of $112,295).

The incremental cost per QALY gained of funded review versus no test (and therefore no treatment) almost always remained the same as the base case results of $67,247. This is because the cost-effectiveness of retrieve and review in this context depends upon the cost-effectiveness of the treatment being initiated. This can be seen when the incremental cost and/or incremental effectiveness of the treatment is changed in sensitivity analysis.

A similar pattern is observed in the sensitivity analyses where funded retrieve and review is compared with funded retrieve and review. This is because the incremental impact of the proposed MBS service is essentially the same – more patients are gaining access to PBS funded treatment (in the case of unfunded review being the comparator it is because timeliness allows more patients to gain access to treatment). In the circumstance where funded retrieve and review attracts no MBS benefit – and it is simply assumed the test will be delivered in time – the incremental cost per QALY gained is $60,000. This is completely consistent with the original PBAC/MSAC decision where there most likely was a built in assumption that the necessary testing will be performed in a timely manner and there was no explicit cost for the retrieve and review process. Were an explicit cost for retrieve and review built in to the original assessment of cost-effectiveness of the co-dependent technologies, the economic model predicts this incremental cost per QALY would have been $67,247.

SECTION E FINANCIAL IMPLICATIONS

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. As noted in the Final Protocol and discussed in Section A above, the patient population that will predominantly benefit from this service are patients with cancers that may be eligible for targeted therapies. Cancers are characterised by genetic mutations, some of which can be used to inform patient selection for specific target therapies. This improves patient outcomes and, equally importantly, can prevent 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. *See the Final Protocol and Section A for further description of the proposed service.*

As specified in the Final Protocol, the proposed service is primarily to be used in conjunction with five pathology tests (MBS item numbers 73332, 73336, 73337, 73338 and 73341) which are used to determine eligibility for co-dependent PBS medications, as summarised in Table 41 below. In addition to these five tests included in the Final Protocol, MBS item 73342 was added in April 2016 for HER2 in gastric cancer (see Table 41).

The proposed service may be also used to assist other pathology tests, e.g., diagnosis of rare non-cancer genetic indications. However, as also acknowledged in the Final Protocol, the extent of usage for these indications is expected to be small, and thus not considered in the current Section E. *More importantly, the proposed MBS item is not limited to the existing tests as more are being considered for listing currently and will continue to be considered in the future by MSAC.* However, it is difficult to predict the extent of potential usage associated with future MBS listing; to this end, the current Section E will focus on the estimated extent of usage associated with the currently available pathology tests enlisted in Table 41 below. *Sensitivity analysis presented in Section E.6 considers the proposed service's usage associated with a possible future expansion of relevant pathology tests on the MBS.*

Table 41 Pathology tests currently available on the MBS that are potentially relevant to the proposed retrieval and review of archival tissue by a pathologist

MBS item code	Examined gene and indication	Treatment administered	Annual incidence of the treated cancer in 2012, any disease stages
73332 (available on the MBS since May 2012)	Human epidermal growth factor receptor 2 (HER2) in women with breast cancer[a]	Trastuzumab	15,166 [b]
73336 (available on the MBS since December 2013)	BRAF V600 gene mutation in patients with unresectable stage IIIc or metastatic stage IV cutaneous melanoma	Dabrafenib	12,036 [b]
73337 (available on the MBS since January 2014)	Epidermal growth factor receptor (EGFR) testing in patients with Stage IIIb or Stage IV non-squamous non-small cell lung cancer	Erlotinib and gefitinib	5,791 [c]
73338 (available on the MBS since April	Rat sarcoma (RAS) oncogene mutation testing in patients with Stage IV colorectal	Cetuximab or panitumumab	14,958 [b]

MBS item code	Examined gene and indication	Treatment administered	Annual incidence of the treated cancer in 2012, any disease stages
2014)	cancer		
73341 (available on the MBS since July 2015)	Anaplastic lymphoma kinase (ALK) immunoreactivity testing for patients with Stage IIIb or Stage IV non-squamous non-small cell lung cancer and who are negative for mutations of EGFR	Crizotinib	5,791 [c]
73342 (available on the MBS since April 2016)	Human epidermal growth factor receptor 2 (HER2) in metastatic adenocarcinoma of the stomach or gastro-oesophageal junction	Trastuzumab	2,118 (stomach) / 1,460 (oesophagus) [b]

a. 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, e.g., for patients presenting with metastatic disease.

b. The 2016 Australian Cancer Incidence and Mortality (ACIM) book. The presented data related to the overall incidence in Australia; NOT related to the number of patients who are eligible for the target therapies.

c. The 2016 Australian Cancer Incidence and Mortality (ACIM) book. The presented data related to the overall incidence of non-squamous non-small cell lung cancer; NOT related to the number of patients who are eligible for the target therapies. "Lung cancer in Australia: an overview" (AIHW 2011) suggested 53% of all lung cancer to be non-squamous non-small cell subtypes; 5791 = 53% x 10926 (based on the ACIM data).

In the current analysis, the historical and current use of the relevant pathology tests is examined to estimate an underlying "demand" for the retrieval and review of archival tissue by a pathologist on the MBS. Estimated uptake of the proposed service for each of the relevant pathology test (i.e., likely proportion of the pathology test that is assisted by the proposed service) is then applied to derive usage estimates of the proposed service.

It is acknowledged that there may be some cost offsets (or savings) for the MBS and for the wider Australian healthcare system should the proposed service be added to the MBS, e.g., less repeat tests and a reduced risk of inappropriate use of a target therapy. While the presence of these potential cost savings is acknowledged, they are not explicitly quantified in the current analysis due to a lack of reliable relevant evidence to do so. Net cost estimates presented in the current analysis should be nonetheless considered as being conservative, representing an overestimation (likely to be to a small extent) of net cost impacts of the proposed listing to the Australian healthcare system. Also, the proposed service has been well established in Australia, and is currently paid for by the laboratories themselves (i.e., the associated costs are being absorbed) or charged to patients. While a successful listing will provide cost savings to them, these are not savings to the healthcare system per se and thus are not explicitly captured in the current analysis.

E.1 JUSTIFICATION OF THE SELECTION OF SOURCES OF DATA

As set out above, the current analysis will examine the historical and current usage of the six pathology tests with which the retrieval and review of archival tissue by a pathologist will be used in conjunction on the MBS (see Table 33). Relevant utilisation statistics are obtained from MBS Item Statistics Reports for analysis.[1] An estimated proportion of each pathology test assisted by the

[1] http://medicarestatistics.humanservices.gov.au/statistics/mbs_item.jsp

proposed service (i.e., an uptake rate) is informed by the Final Protocol (where available).

An alternative estimation method of epidemiological approach (i.e., based on the cancer incidence) was considered as unreliable and being associated with a greater uncertainty. This is especially because these pathology tests are generally used for a small subgroup of patients who have an advanced disease but are considered eligible for a further active treatment. Estimating an eligible patient population size in this context hence requires a wide range of data inputs including cancer incidence, treatment rate, treatment options and their use, rate of disease progression, mortality etc. It is believed that the current approach based on the available utilisation data for relevant pathology test offers a simple and transparent methodology with superior estimation accuracy.

E1.1 PROJECTED USE OF RELEVANT PATHOLOGY TESTS ON THE MBS

Table 42 and Figure 26 present the historical use of pathology tests with which the retrieval and review of archival tissue by a pathologist will be used in conjunction on the MBS. Except for 73332, limited longitudinal data are available for these tests because they were added to the MBS relatively only recently. This is especially the case for 73341 and 73342.

Table 42 Historical use of relevant pathology tests on the MBS

Year	2012	2013	2014	2015	2016
73332 (HER2 in breast cancer)	345	9,709	13,161	12,882	12,902
73336 (BRAF v600 in melanoma)			487	1548	1966
73337 (EGFR in non-squamous non-small cell lung cancer)			399	2659	3443
73338 (RAS in colorectal cancer)			52	1462	2844
73341 (ALK in non-squamous non-small cell lung cancer)					191
73342 (HER2 in gastric cancer)					46
All combined	345	9,709	14,099	18,551	21,392

Source: MBS Item Statistics Reports (accessed August 2016)
Note: Financial year data are used to maximise the available data.
Abbreviations: ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor 2; RAS =Rat sarcoma; MBS = Medicare Benefits Schedule.

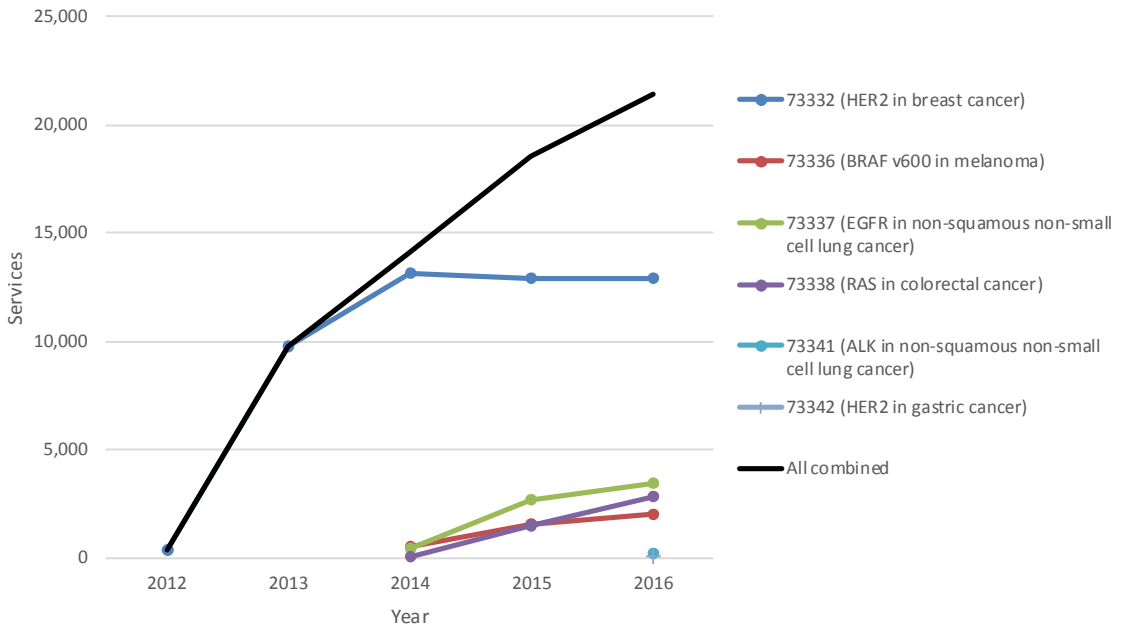

Figure 26 Historical use of relevant pathology tests on the MBS

Source: MBS Item Statistics Reports (accessed August 2016); see Table 42 above.
Abbreviations: ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor 2; RAS =Rat sarcoma; MBS = Medicare Benefits Schedule.

The available 73332 data (for HER2 testing in breast cancer) suggest that its usage quickly stabilised after 2-3 years of listing. This may reflect the presence of a very high clinical need / interest for an effective target treatment in a specialised therapeutic area and with a relatively stable breast cancer incidence over time. That is, the uptake for a new target treatment and associated services like a gene testing is very high and reaches a "full" uptake soon after the introduction to the market because doctors / patients are very informed and motivated to use a new treatment.

This pattern of uptake may be also expected for other pathology tests that were recently added to the MBS listing in the next 2-3 years because these tests and treatments are also for patients with an advanced progressive cancer.

For the base case analysis, the following usage projections are assumed for pathology tests currently subsidised under MBS item codes 73332, 73336, 73337 and 73338, as shown in Table 43. These usage projections reflect an assumption that the use of 73332 remains at its 2016 level (see Table 42). For 73336, 73337 and 73338, a small growth in 2017 is added as suggested by the available historical data; but their usage are assumed to stabilise thereafter (as supported by the available 73332 data as discussed above).

Table 43 Projected use of pathology tests 73332, 73336, 73337 and 73338 on the MBS

Year	2016	Estimated usage for 2017 to 2021 (Year 1 to Year 5)
73332 (HER2 in breast cancer)	12,902	12,902
73336 (BRAF v600 in melanoma)	1,966	2,400 [a]
73337 (EGFR in non-squamous non-small cell lung cancer)	3,443	4,200 [a]
73338 (RAS in colorectal cancer)	2,844	4,200 [a]

Note: See "Section E MSAC Assessment Report _1331.1.xls"

a. Adjusted for a small growth expected during the 2017 period, as suggested by their historical usage. The assumed growths are roughly based on their 2015-2016 growth amounts.

Abbreviations: EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor 2; RAS =Rat sarcoma; MBS = Medicare Benefits Schedule.

The above estimation approach based on the historical MBS statistics was not appropriate for 73341 and 73342, as they are only recently added to the MBS and thus the available utilisation data were premature in informing the likely steady state usage level. For the purpose of this analysis, the steady state 73341 usage is assumed to 85% of the usage expected for 73337 (also for non-squamous NSCLC); based on an estimate that 10-20% of patients tested for EGFR return a negative result (see the Final Protocol). For 73342, the relevant Public Summary Document (Application no. 1250.1) is inspected (see Table 45 below). It was suggested that less than 1000 patients would receive this test for the gastric cancer indication, and this estimate is employed by the current analysis.

Table 44 hence presents the estimated extent of use of pathology tests that would be potentially assisted by the proposed service on the MBS during the first five years.

Table 44 Projected use of relevant pathology tests, Year 1 - 5

Year	Year 1	Year 2	Year 3	Year 4	Year 5	Source
73332 (HER2 in breast cancer)	12,902	12,902	12,902	12,902	12,902	See Table 43
73336 (BRAF v600 in melanoma)	2,400	2,400	2,400	2,400	2,400	
73337 (EGFR in non-squamous non-small cell lung cancer)	4,200	4,200	4,200	4,200	4,200	
73338 (RAS in colorectal cancer)	4,200	4,200	4,200	4,200	4,200	
73341 (ALK in non-squamous non-small cell lung cancer)	3,570	3,570	3,570	3,570	3,570	Assumed to be 85% of 73337; based on the estimated % of negative EGFR results
73342 (HER2 in gastric cancer)	1,000	1,000	1,000	1,000	1,000	As per PSD (App no. 1250.1)
All combined	28,272	28,272	28,272	28,272	28,272	Calculated

Note: See "Section E MSAC Assessment Report _1331.1.xls"

Abbreviations: ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor 2; RAS =Rat sarcoma; MBS = Medicare Benefits Schedule; PSD = Public Summary Document.

It is acknowledged that the derivation of projected usage for the relevant pathology tests in the aforementioned manner may be considered as being simplistic, although it reflects the paucity of relevant evidence to inform the necessary estimation process. Inspection of relevant PBSs nonetheless suggests that the current estimates are either well supported or more realistic and reasonable than those included in the PSDs, as shown in Table 45 below. Where a large disparity exists (e.g., for 73336, 73337 and 73338), the numbers quoted in PSDs were based on unrealistic or poorly applicable epidemiological data and clearly not in line with the historical usage (although still limited) so far on the MBS (see Table 45).

Table 45 Usage estimates included in PSD for the relevant pathology tests

Year	Estimated usage per annum quoted in PSD	Note / source
73332 (HER2 in breast cancer)	NA	Application 1230 (seeking an amendment to the then existing listing to include neoadjuvant cases) estimated additional 1,189 cases due to the recommended amendment. The current listing is wider. The MBS statistics and the breast cancer incidence data suggest a large % of patient receive this test, and the usage is unlikely to grow further.
73336 (BRAF v600 in melanoma)	<2,000	Application 1172. The relevant target therapy for this application was vemurafenib (not currently available on the PBS; an alternative to dabrafenib)
73337 (EGFR in non-squamous non-small cell lung cancer)	<8,000	Application 1173 (relevant to the first-line use of erlotinib; the current PBS listing is without reference to any line of therapy). The quoted estimate is likely to be overestimate in light of the available incidence data (less than 6000 non-squamous NSCLC; all stages) and the historical usage (see Table 41 and Table 42).
73338 (RAS in colorectal cancer)	6,747	Application 1363. The quoted estimate is likely to be overestimate because it is based on the estimated number of all metastatic colorectal incidence; a large proportion of advanced diseases may not be considered eligible for cetuximab or panitumumab (e.g., poor performance status thus opt for palliative care instead etc).
73341 (ALK in non-squamous non-small cell lung cancer)	<10,000	Application 1250.1. The quoted estimate is likely to be overestimate in light of the available incidence data (less than 6000 non-squamous NSCLC; all stages) and the historical usage of 73337 (see Table 41 and Table 42). Also, its use is for patients who are negative for mutations of EGFR (73337)
73342 (HER2 in gastric cancer)	<1,000	Application 1163 estimated a 5-year total of <5000 patients; annualised to <1000 for this table

Source: MBS Item Statistics Reports (accessed August 2016)
Abbreviations: ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor 2; RAS =Rat sarcoma; NSCLC = non-small cell lung cancer; MBS = Medicare Benefits Schedule; PSD = Public Summary Document.

To supplement the budget impact evidence to be considered by the evaluators and the MSAC, a series of sensitivity analyses is performed based on an estimated aggregate use for all pathology tests (see "All combined" in Table 42 and Figure 26 above). The presented sensitivity analyses will explore two projection scenarios, as shown in Figure 27 and Figure 28 below.

Results from these sensitivity analyses are presented in Section E.6 below. Alternative assumptions explored by these analyses will result in usage estimates that are greater than the base case assumption described above (see Table 43). They can be also interpreted as capturing additional pathology tests that are yet to be added to the MBS but may become available in the future, generating additional demand for the retrieval and review of archival tissue.

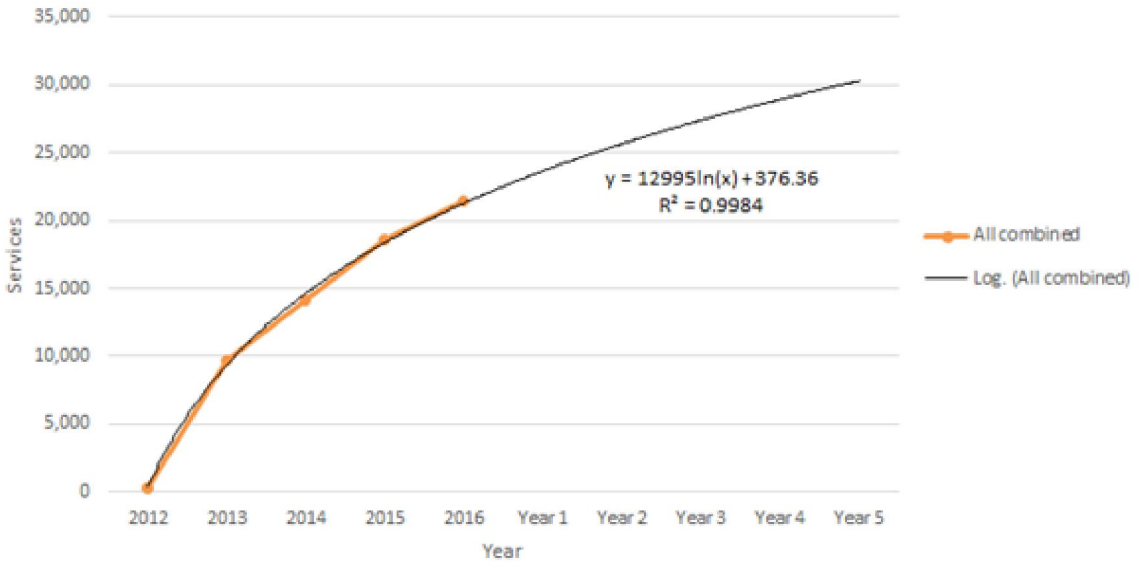

Figure 27 Projected use of pathology tests potentially assisted by the proposed service, all tests combined ; Logarithmic extrapolation

Note: See "Section E MSAC Assessment Report _1331.1.xls"

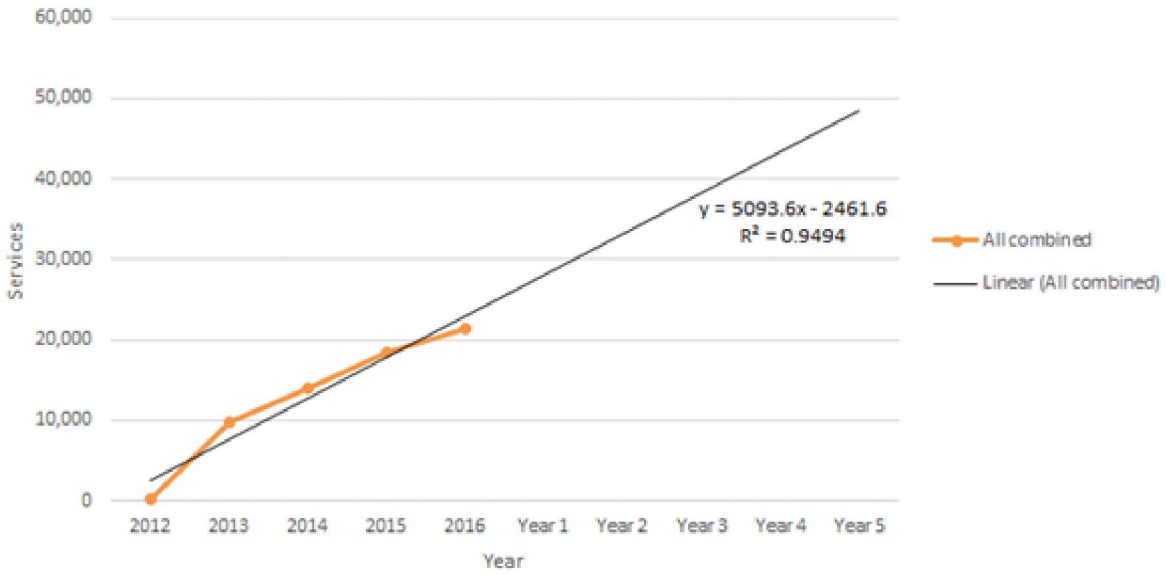

Figure 28 Projected use of pathology tests potentially assisted by the proposed service, all tests combined ; Linear extrapolation

Note: See "Section E MSAC Assessment Report _1331.1.xls"

E1.2 PROPORTIONS OF PATHOLOGY TESTS ASSISTED BY THE PROPOSED SERVICE

Estimation of the proportion of each relevant pathology test assisted by the retrieval and review of archival tissue by a pathologist is primarily informed by the Final Protocol. It was noted that the majority of 73332 tests (HER2 in breast cancer) are performed at the time of diagnosis; thus not requiring a subsequent retrieval and review. The Final Protocol suggested that the test may be required retrospectively during the course of patient care, e.g., for patients presenting with metastatic disease; but this is expected to be only applicable to a small proportion of the cases. The current analysis assumes that 5% of the total 73332 tests are to be assisted by the proposed service.

For 73341 (ALK in non-squamous NSCLC), the proportion is assumed to be equal to 73337 (EGFR in non-squamous NSCLC). Of note, it may be possible that one retrieval and review episode could assist 73337 and 73341 simultaneously in some patients. Accounting for these tests separately as done here may lead to overestimation of the total costs.

For 73342 (HER2 in gastric cancer), the proportion assumed for 73332 (HER2 in breast cancer) is unlikely to be applicable because the relevant target therapy is restricted for use in advanced disease. For the purpose of this analysis, 50% of all tests are assumed to be assisted by the retrieval and review of archival tissue.

Table 46 Estimated proportion of pathology tests assisted by the proposed service

Year	Estimated proportion	Note / source
73332 (HER2 in breast cancer)	5%	Assumption; the Final Protocol suggests that the test is generally performed upon diagnosis, thus not requiring a subsequent retrieval and review.
73336 (BRAF v600 in melanoma)	50%	As per the Final Protocol.
73337 (EGFR in non-squamous non-small cell lung cancer)	30%	As per the Final Protocol.
73338 (RAS in colorectal cancer)	80%	As per the Final Protocol.
73341 (ALK in non-squamous non-small cell lung cancer)	30%	Assumed to be same as 73337
73342 (HER2 in gastric cancer)	50%	Assumption
All combined, weighted average	28%	Calculated based on the usage projections in Table 43.

Note: See "Section E MSAC Assessment Report _1331.1.xls"
Abbreviations: ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor 2; RAS =Rat sarcoma.

It is acknowledged that expected uptakes are largely based on the expert opinion and experience due to a lack of relevant data. The assumptions can be easily altered in the attached spreadsheet ("Section E MSAC Assessment Report _1331.1.xls"), allowing the evaluators / ESC / MSAC to explore alternative scenarios.

E.2 USE AND COSTS OF THE PROPOSED SERVICE

Combining information presented in Table 43 and Table 46 above, the estimated number of service episodes for retrieve / review of archived tissue each year during the first five years of listing can be derived, as shown in Table 47 below.

It is estimated that, in total, approximately 8000 episodes of the retrieval and review of archival tissue are performed in relation to the existing six pathology tests considered in the current analysis.

Table 47 Estimated extent of use of the proposed service on the MBS

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of 73332 tests (HER2 in breast cancer)	12,902	12,902	12,902	12,902	12,902
- % assisted by the proposed service	5%				
- Number of service episodes provided	645	645	645	645	645
Number of 73336 tests (BRAF v600 in melanoma)	2,400	2,400	2,400	2,400	2,400
- % assisted by the proposed service	50%				
- Number of service episodes provided	1,200	1,200	1,200	1,200	1,200
Number of 73337 tests (EGFR in non-small cell lung cancer)	4,200	4,200	4,200	4,200	4,200
- % assisted by the proposed service	30%				
- Number of service episodes provided	1,260	1,260	1,260	1,260	1,260
Number of 73338 tests (RAS in colorectal cancer)	4,200	4,200	4,200	4,200	4,200
- % assisted by the proposed service	80%				
- Number of service episodes provided	3,360	3,360	3,360	3,360	3,360
Number of 73341 tests (ALK in non-squamous non-small cell lung cancer)	3,570	3,570	3,570	3,570	3,570
- % assisted by the proposed service	30%				
- Number of service episodes provided	1,071	1,071	1,071	1,071	1,071
Number of 73342 tests (HER2 in gastric cancer)	1,000	1,000	1,000	1,000	1,000
- % assisted by the proposed service	50%				
- Number of service episodes provided	500	500	500	500	500
Total	**8,036**	**8,036**	**8,036**	**8,036**	**8,036**

Note: See "Section E MSAC Assessment Report _1331.1.xls"
Abbreviations: ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor 2; RAS =Rat sarcoma; MBS = Medicare Benefits Schedule.

The proposed fee is $150.00 (or at 85% benefit = $127.50; at 75% benefit = $112.50). Costs to the MBS are based on the expected utilisation of the service in inpatients (75% benefit) and outpatients (85% benefit). The expected utilisation of the service in each of these two settings are based on that associated with the corresponding test (Table 48).

Table 48 Utilisation of molecular testing on the MBS in inpatients and outpatients (2015/16)

MBS item	In Hospital	Out of Hospital	Total
73332 (HER2 in breast cancer)	7849 (61%)	5053 (39%)	12,902 (100%)
73336 (BRAF v600 in melanoma)	348 (18%)	1618 (82%)	1966 (100%)
73337 (EGFR in non-squamous non-small cell lung cancer)	1015 (29%)	2428 (71%)	3443 (100%)
73338 (RAS in colorectal cancer)	224 (8%)	2620 (92%)	2844 (100%)
73341 (ALK in non-squamous non-small cell lung cancer)	35 (18%)	156 (82%)	191 (100%)
73342 (HER2 in gastric cancer)	4 (9%)	42 (91%)	46 (100%)

Source: Data provided by Department of Health; Pathology & Schedule Management Team (2 September 2016)

The total annual cost to the MBS benefit is estimated to be approximately $1.0 million, with approximately 82% ($835,815) of this cost accrued in patients claiming an 85% rebate and 18% ($166,577) in patients claiming a 75% rebate (see Table 49). *In practice, the "uptake" of the proposed service may be more gradual; reaching $1.0 million in 2-3 years after the listing. Nonetheless, the uptake is likely to be very rapid for the proposed service because it has been performed in practice already despite the lack of a formal MBS rebate.*

Table 49 Estimated costs of the proposed service to the MBS

Year	Year 1	Year 2	Year 3	Year 4	Year 5
To assist 73332 (HER2 in breast cancer)					
- Number of MBS services	645	645	645	645	645
- Services at 85% benefit (39%)	253	253	253	253	253
- Services at 75% benefit (61%)	392	392	392	392	392
To assist 73336 (BRAF v600 in melanoma)					
- Number of MBS services	1,200	1,200	1,200	1,200	1,200
- Services at 85% benefit (82%)	988	988	988	988	988
- Services at 75% benefit (18%)	212	212	212	212	212
To assist 73337 (EGFR in non-squamous non-small cell lung cancer)					
- Number of MBS services	1,260	1,260	1,260	1,260	1,260
- Services at 85% benefit (71%)	889	889	889	889	889
- Services at 75% benefit (29%)	371	371	371	371	371
To assist 73338 (RAS in colorectal cancer)					
- Number of MBS services	3,360	3,360	3,360	3,360	3,360
- Services at 85% benefit (92%)	3,095	3,095	3,095	3,095	3,095
- Services at 75% benefit (8%)	265	265	265	265	265
To assist 73341 (ALK in non-squamous non-small cell lung cancer)					
- Number of MBS services	1,071	1,071	1,071	1,071	1,071
- Services at 85% benefit (82%)	875	875	875	875	875
- Services at 75% benefit (18%)	196	196	196	196	196
To assist 73342 (HER2 in gastric cancer)					
- Number of MBS services	500	500	500	500	500
- Services at 85% benefit (91%)	457	457	457	457	457

Year	Year 1	Year 2	Year 3	Year 4	Year 5
- Services at 75% benefit (9%)	43	43	43	43	43
Totals					
Number of MBS services					
- Services at 85% benefit	6,555	6,555	6,555	6,555	6,555
- Services at 75% benefit	1,481	1,481	1,481	1,481	1,481
Total	8,036	8,036	8,036	8,036	8,036
Total costs 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	$1,002,392	$1,002,392	$1,002,392	$1,002,392	$1,002,392

Note: See "Section E MSAC Assessment Report _1331.1.xls"
Abbreviations: ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor 2; RAS =Rat sarcoma; MBS = Medicare Benefits Schedule.

E.3 Changes in Use and Cost of Other Medical Services

There may be some cost offsets for the MBS should the proposed service be added to the listing. For example, the proposed service will facilitate the use of archived tissue in place of a repeat biopsy in some patients, thereby reducing the number of repeat biopsy tests overall. The extent of cost offsets arising from these improved efficiencies in clinical practice is uncertain but likely to be small (while the presence of these offsets is acknowledged in this assessment, and some are explicitly considered in Section D). As also discussed in the Final Protocol, the proposed service of retrieval / review of archival tissue for further pathology testing widely takes place already in the Australian clinical practice, although the associated costs are not currently met publicly. While it is important to clarify the service's eligibility for a MBS subsidisation, as considered in the current assessment, and its addition to the MBS listing will offer improved clinical efficiencies, net changes in the use of other medical services are expected to be relatively small. Also, no reliable data are available to perform an accurate estimation of possible financial implications to the MBS.

For these reasons, the potential changes in the use and cost of other medical services are not explicitly quantified in the current Section E. This will be nonetheless lead to a set of conservative estimates being presented to the MSAC (i.e., a slight overestimation of net budgetary impacts of the proposed service).

E.4 Financial Implications for the MBS

Table 49 above estimated that the total annual cost is estimated to be approximately $1.0 million in the fifth year of listing.

E.5 Financial Implications for Government Health Budgets

The presence of potential cost savings to the wider Australian healthcare system is acknowledged in this assessment (and considered in Section D), e.g., an improvement in patient selection for a target therapy may offer improved health outcomes and cost savings. However, for the same reasons as those discussed in Section E.3, potential cost savings to other government health budgets are not explicitly quantified in the current Section E. This approach will lead to a set of conservative estimates being presented to the MSAC (i.e., a slight overestimation of net financial impacts of the proposed service).

E.6 Identification, Estimation and Reduction of Uncertainty

Section E.1 above discussed that some uncertainties remain with the projected future use of relevant pathology tests. Also, there will be new additions to the MBS that can be potentially assisted by the proposed service.

As set out above, sensitivity analysis is presented here to explore two projection scenarios, as shown in Figure 27 and Figure 28 above (presented again in Figure 29 and Figure 30 below for convenience). These scenarios reflect an assumption that the MBS use of pathology tests that are relevant to the proposed service continue to grow with a historically observed trend. Two alternative extrapolation methods are considered; logarithmic extrapolation (see Figure 29) and linear extrapolation (see Figure 30).

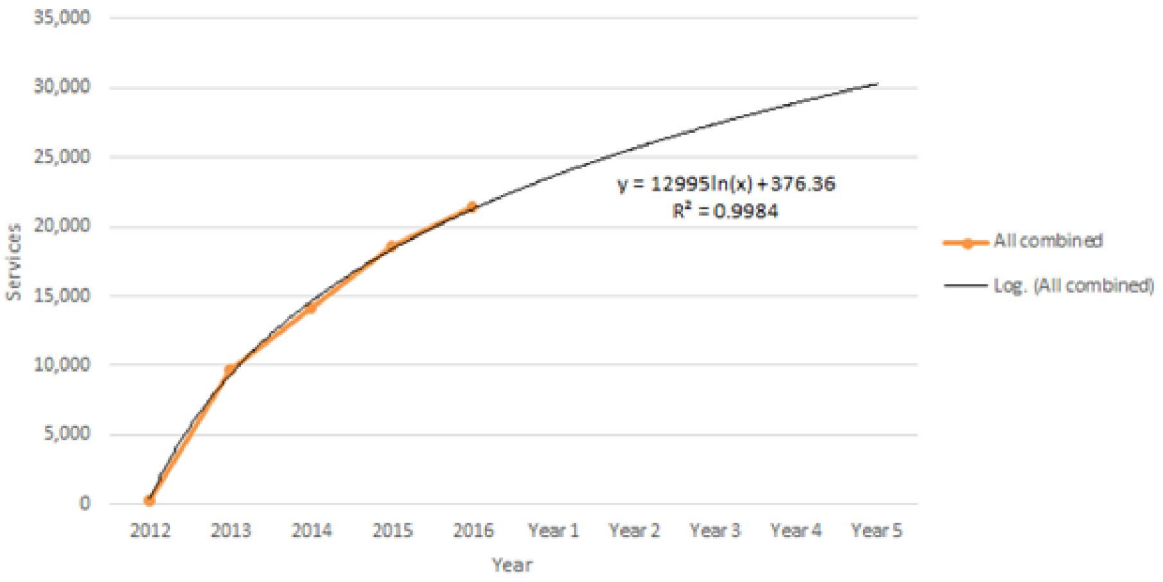

Figure 29 Projected use of pathology tests potentially assisted by the proposed service, all tests combined; Logarithmic extrapolation

Note: See "Section E MSAC Assessment Report _1331.1.xls"

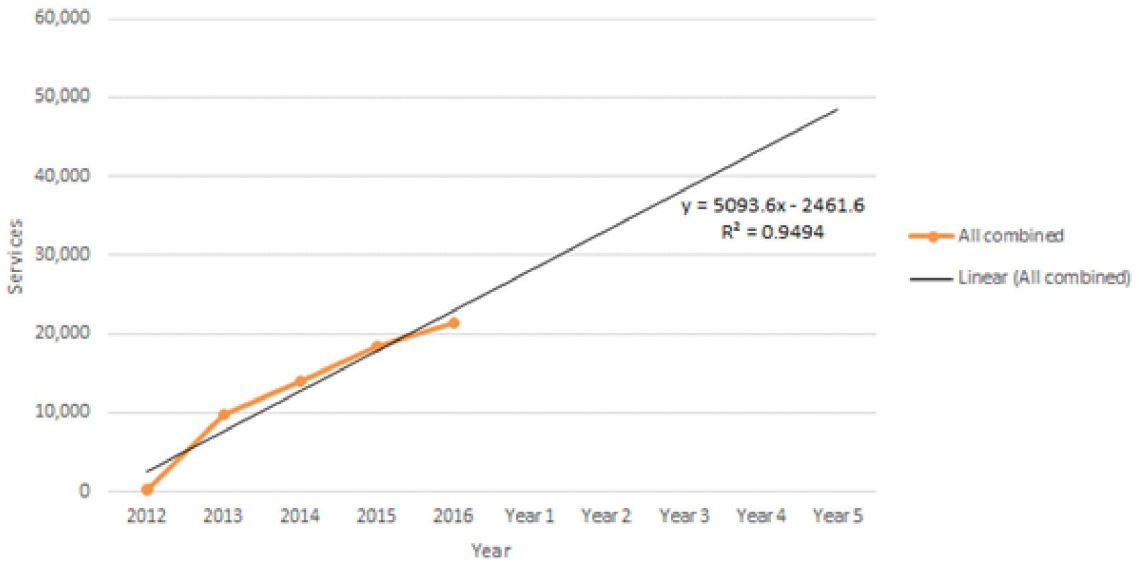

Figure 30 Projected use of pathology tests potentially assisted by the proposed service, all tests combined; Linear extrapolation

Note: See "Section E MSAC Assessment Report _1331.1.xls"

Results from sensitivity analyses are presented in Table 50 and Table 51. As shown in Table 46 above, on average 28% of the existing six pathology tests are to be assisted by the proposed service. This proportion may also change as new pathology tests are added to the MBS, which may also attract the proposed service. The current analyses explore 40% and 60% for this parameter, as shown in Table 50 and Table 51.

The utilisation split between inpatient and outpatient is assumed to be 82% and 18%, as derived in the base case calculations above (see Table 49).

When the most "aggressive" usage extrapolation assumption (i.e., linear extrapolation with 60% being assisted by the proposed service) is applied, it is estimated that 29,085 episodes of the proposed service are used at the total MBS cost of $4.4 million in the fifth year of listing. *It should be noted that these aggressive assumptions may become realistic only if new pathology tests are added to the MBS at the same (or higher) rate as that observed in the previous 5 years (i.e., 4-5 tests). Also, it may be possible that one retrieval and review episode could assist multiple pathology tests if they are for the same indication; indeed, this could happen with the existing 73337 and 73341 (both for advanced non-squamous NSCLC).*

Table 50 Estimated costs of the proposed service to the MBS – sensitivity analysis using a logarithmic extrapolation method

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated pathology test usage, aggregate (see Figure 29)	23,660	25,672	27,407	28,938	30,307
Assuming 28% to be assisted by the proposed service					
- Number of service episodes provided	6,724	7,296	7,789	8,224	8,613
- 85% benefit (82% at $127.50)	$699,373	$758,839	$810,131	$855,373	$895,844
- 75% benefit (18% at $112.50)	$139,384	$151,236	$161,458	$170,475	$178,541
Total	$1,008,637	$1,094,399	$1,168,372	$1,233,622	$1,291,989
Assuming 40% to be assisted by the proposed service					
- Number of service episodes provided	9,464	10,269	10,963	11,575	12,123
- 85% benefit (82% at $127.50)	$984,339	$1,068,035	$1,140,226	$1,203,903	$1,260,864
- 75% benefit (18% at $112.50)	$196,178	$212,858	$227,246	$239,937	$251,289
Total	$1,419,616	$1,540,323	$1,644,437	$1,736,272	$1,818,422
Assuming 60% to be assisted by the proposed service					
- Number of service episodes provided	14,196	15,403	16,444	17,363	18,184
- 85% benefit (82% at $127.50)	$1,476,509	$1,602,052	$1,710,339	$1,805,855	$1,891,297
- 75% benefit (18% at $112.50)	$294,267	$319,288	$340,869	$359,905	$376,934
Total	$2,129,425	$2,310,484	$2,466,655	$2,604,409	$2,727,633

Note: See "Section E MSAC Assessment Report _1331.1.xls"
Abbreviations: MBS = Medicare Benefits Schedule.

Table 51 Estimated costs of the proposed service to the MBS – sensitivity analysis using a linear extrapolation method

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated pathology test usage, aggregate (see Figure 30)	28,100	33,194	38,287	43,381	48,474
Assuming 28% to be assisted by the proposed service					
- Number of service episodes provided	7,986	9,434	10,881	12,329	13,776
- 85% benefit (82% at $127.50)	$830,607	$981,168	$1,131,729	$1,282,291	$1,432,852
- 75% benefit (18% at $112.50)	$165,539	$195,546	$225,553	$255,559	$285,566
Total	$1,197,903	$1,415,043	$1,632,183	$1,849,324	$2,066,464
Assuming 40% to be assisted by the proposed service					
- Number of service episodes provided	11,240	13,277	15,315	17,352	19,390
- 85% benefit (82% at $127.50)	$1,169,045	$1,380,954	$1,592,863	$1,804,773	$2,016,682
- 75% benefit (18% at $112.50)	$232,990	$275,223	$317,456	$359,690	$401,923
Total	$1,686,000	$1,991,616	$2,297,232	$2,602,848	$2,908,464
Assuming 60% to be assisted by the proposed service					
- Number of service episodes provided	16,860	19,916	22,972	26,028	29,085
- 85% benefit (82% at $127.50)	$1,753,568	$2,071,431	$2,389,295	$2,707,159	$3,025,023
- 75% benefit (18% at $112.50)	$349,484	$412,834	$476,184	$539,534	$602,884
Total	$2,529,000	$2,987,424	$3,445,848	$3,904,272	$4,362,696

Note: See "Section E MSAC Assessment Report _1331.1.xls"
Abbreviations: MBS = Medicare Benefits Schedule.

Appendix A Clinical Experts and Assessment Group

Health Expert Standing Panel (HESP) (if allocated)

Member	Expertise or affiliation

Name	Expertise

Assessment group

XXXX

Name	Position

Noted conflicts of interest

There were no conflicts of interest.>

APPENDIX B SEARCH STRATEGIES

TBC

REFERENCES

References in bold are not provided with the submission but can be made available on request

Abdulkareem, F. B., Sanni, L. A., Richman, S. D., Chambers, P., Hemmings, G., Grabsch, H.,. .. Rotimi, O. (2012). KRAS and BRAF mutations in Nigerian colorectal cancers. *West Afr J Med, 31*(3), 198-203.

AIHW. (2011). *Lung cancer in Australia: an overview.* Canberra.

APS. (2013). Money in the archives. *Newsletters.* Feb 2013. Retrieved from http://apsmedbill.com/newsletters/2013-02/money-archives

Arriola, E., Garcia Gomez, R., Diz, P., Majem, M., Martinez Aguillo, M., Valdivia, J.,. .. Barneto, I. C. (2014). *Observational retrospective study to describe the management of advanced epidermal growth factor receptor (EGFR) mutated (M+) non-small cell lung cancer (NSCLC) patients (pts) in Spain (NCT01795352).* Paper presented at the ASCO Annual Meeting Proceedings.

Artru, P., Ducreux, M., Lièvre, A., Guiu, M., Merlin, J. L., Sabourin, J. C.,. .. Laurent-Puig, P. (2012, 1-5 June 2012). *Review of the current status of KRAS mutation testing in France in 2011: The Flash KRAS study.* Paper presented at the ASCO Annual Meeting, Chigaco.

Aubin, F., Gill, S., Burkes, R., Colwell, B., Kamel-Reid, S., Koski, S.,. .. Soulieres, D. (2011). Canadian Expert Group consensus recommendations: KRAS testing in colorectal cancer. *Curr Oncol, 18*(4), e180-184.

Baldotto, C., Lima, A., Siqueira, M., Montella, T., Domingues, P. M., Herchenhorn, D., & Zukin, M. (2013). *Results of epidermal growth factor receptor (EGFR) reflex testing implementation in the Brazilian National Cancer Institute (INCA).* Paper presented at the Journal of Thoracic Oncology.

Bang, Y. J., Van Cutsem, E., Feyereislova, A., Chung, H. C., Shen, L., Sawaki, A.,. .. Kang, Y. K. (2010). Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet, 376*(9742), 687-697. doi:10.1016/s0140-6736(10)61121-x

Beasley, M. B., & Milton, D. T. (2011). ASCO provisional clinical opinion: epidermal growth factor receptor mutation testing in practice. *Journal of Oncology Practice, 7*(3), 202-204.

Bedard, P. L., Oza, A. M., Tsao, M.-S., Leighl, N. B., Shepherd, F. A., Chen, E. X.,. .. Clarke, B. (2013). *Princess Margaret Cancer Centre (PMCC) Integrated Molecular Profiling in Advanced Cancers Trial (IMPACT) using genotyping and targeted next-generation sequencing (NGS).* Paper presented at the ASCO Annual Meeting Proceedings.

Bibeau, F., Frugier, H., Crapez, E., Lamy, P., Ychou, M., & Boissière-Michot, F. (2010). *KRAS mutation testing in patients with metastatic colorectal carcinoma: An 18-month experience emphasizing the risk of false-negative results.* Paper presented at the ASCO Annual Meeting Proceedings.

Bibeau, F., Louvet, C., Afchain, P., Mitry, E., Artru, P., & André, T. (2012). Observational study on conditions for access to the analysis of KRAS mutation in patients with metastatic colorectal cancer receiving panitumumab treatment. *Bulletin du cancer, 99*(7-8), 743.

Boleij, A., Tembuyser, L., Taylor, A., Kafatos, G., Jenkins-Anderson, S., Tack, V.,. .. van Krieken, H. (2015). PD-015A survey on current RAS-mutation testing practices in Europe. *Annals of Oncology, 26*(suppl 4), iv105. doi:10.1093/annonc/mdv234.14

Butt, M. A., Gandy, M., Haidry, R. J., Bloom, E. S., Mackie, S., Khan, M. S.,. .. Banks, M. R. (2013). Mo1134 HER2 Positivity in Metastatic Upper Gastrointestinal Tumours in a Large Multi-Centre UK Cohort Identifies Similar Positivity Rates but Different Trends Than Previously Reported and Suggests New Potential Avenues for HER2 Therapies. *Gastroenterology, 144*(5), S-587-S-588.

Cankovic, M., Whiteley, L., Michalowski, S., Stone, C., Zarbo, R., & Chitale, D. (2013). *Predictive Molecular Markers in Lung Cancer-80% Decrease in Diagnosis to Treatment Decision Times by Streamlining EGFR and ALK Testing Protocols.* Paper presented at the LABORATORY INVESTIGATION.

Cankovic, M., Whiteley, L., Stone, C., Zarbo, R., & Chitale, D. (2013). *EGFR/ALK Testing in Lung Cancer: Streamlining Preanalytic Phase Resulted in 80% Decrease in Diagnosis to Treatment Decision Times.* Paper presented at the JOURNAL OF MOLECULAR DIAGNOSTICS.

CAP. (2015). *Guideline on the Evaluation of Molecular Markers for Colorectal Cancer Expert Panel Draft Recommendations Summary for Open Comment Period* Retrieved from

CAP. (2016). *Medicare Physician Fee Schedule: Comparison of 2016 RVUs (Updated July 2016) and Proposed 2017 RVUs (Released July 2016)*. Retrieved from http://www.cap.org/ShowProperty?nodePath=/UCMCon/Contribution%20Folders/WebContent/pdf/proposed-2017-fee-schedule-impact-table.pdf.

Carotenuto, P., Roma, C., Rachiglio, A. M., Tatangelo, F., Pinto, C., Ciardiello, F.,. .. Normanno, N. (2010). Detection of KRAS mutations in colorectal carcinoma patients with an integrated PCR/sequencing and real-time PCR approach. *Pharmacogenomics, 11*(8), 1169-1179. doi:10.2217/pgs.10.86

Chretien, A. S., Harle, A., Meyer-Lefebvre, M., Rouyer, M., Husson, M., Ramacci, C.,. .. Merlin, J. L. (2013). Optimization of routine KRAS mutation PCR-based testing procedure for rational individualized first-line-targeted therapy selection in metastatic colorectal cancer. *Cancer Med, 2*(1), 11-20. doi:10.1002/cam4.47

Ciardiello, F., Tejpar, S., Normanno, N., Mercadante, D., Teague, T., Wohlschlegel, B., & Van Cutsem, E. (2011). Uptake of KRAS mutation testing in patients with metastatic colorectal cancer in Europe, Latin America and Asia. *Target Oncol, 6*(3), 133-145. doi:10.1007/s11523-011-0181-x

Dantes, M., von Weyhern, C., Rosenberg, R., Hoefler, H., & Fend, F. (2010). *Role of K-ras Mutations and Activation of the EGFR-Signalling Pathway in Colorectal Carcinoma.* Paper presented at the LABORATORY INVESTIGATION.

Dingemans, A.-M. C., Smit, E. F., Derks, J., Mellema, W., Heideman, D., Van Suylen, R., & Thunnissen, E. (2011). Predictive value of KRAS mutations in advanced non-small cell lung cancer (NSCLC) patients (pts) treated with chemotherapy (CT). *Cancer Research, 71*(8 Supplement), 340-340.

Ducreux, M., Phelip, J., Andre, T., Asselain, B., Senellart, H., Younes, W.,. .. Bennouna, J. (2011). 6112 POSTER Health-related Quality of Life at 12 Months in Patients With Metastatic Colorectal Cancer (mCRC) Initiating a Treatment With Bevacizumab (Bv) Plus Chemotherapy (CT)–Results From the CONCERT French Non Interventional Study. *European Journal of Cancer, 47*, S425-S426.

Ellis, P. M., Verma, S., Sehdev, S., Younus, J., & Leighl, N. B. (2013). Challenges to implementation of an epidermal growth factor receptor testing strategy for non-small-cell lung cancer in a publicly funded health care system. *J Thorac Oncol, 8*(9), 1136-1141. doi:10.1097/JTO.0b013e31829f6a43

Fergusson, S., Nelson, J., McCusker, G., & Sloan, S. (2009). Local efficiency of HER2 measurement and its effect on oncological decision making. *European Journal of Surgical Oncology (EJSO), 35*(11), 1218-1219.

Goom, J., Jasani, B., & Barrett-Lee, P. (2012). *Factors Affecting Turnaround Time for HER2 Reporting in South East Wales Cancer Network (SEWCN).* Paper presented at the JOURNAL OF PATHOLOGY.

Gracia, M., Majem, M., Aguillo, M. M., Banaclocha, N. M., Provencio, M., Arriola, E.,. .. Sureda, B. M. (2011). 3529 POSTER Effect of Sample Type and Turnaround Time (TAT) on the Feasibility of Non-Small Cell Lung Cancer (NSCLC) Epidermal Growth Factor Receptor (EGFR) Mutation Testing in Routine Clinical Practice: Results From the Spanish REASON Study. *European Journal of Cancer, 47*, S255.

Hagemann, I. S., Devarakonda, S., Lockwood, C. M., Spencer, D. H., Guebert, K., Bredemeyer, A. J.,. .. Govindan, R. (2015). Clinical next-generation sequencing in patients with non-small cell lung cancer. *Cancer, 121*(4), 631-639. doi:10.1002/cncr.29089

Halbfass, V., Falk, M., Prenzel, R., Dercken, H., Scriba, D., Tiemann, M., & Griesinger, F. (2011). *P2.233 Incidence of molecular targets (egfr-mutation, eml4-alk, braf and kras) in metastatic nsclc in a certified lung cancer hospital.* Paper presented at the 14th World Council on Lung Cancer, Amsterdam.

Iyer, S. S., Olsen, B., & Hrinczenko, B. (2012). *Biopsy Method And Sample Adequacy For Molecular Testing In Advanced Non Small Cell Lung Cancer.* Paper presented at the JOURNAL OF THORACIC ONCOLOGY.

Janssens, A., De Droogh, E., Lefebure, A., Kockx, M., Pauwels, P., Germonpre, P., & van Meerbeeck, J. P. (2014). Routine implementation of EGFR mutation testing in clinical practice in Flanders: 'HERMES' project. *Acta Clin Belg, 69*(2), 92-97. doi:10.1179/0001551214z.00000000029

Jonker, D. J., O'Callaghan, C. J., Karapetis, C. S., Zalcberg, J. R., Tu, D., Au, H. J.,. .. Moore, M. J. (2007). Cetuximab for the treatment of colorectal cancer. *N Engl J Med, 357*(20), 2040-2048. doi:10.1056/NEJMoa071834

Karapetis, C. S., Khambata-Ford, S., Jonker, D. J., O'Callaghan, C. J., Tu, D., Tebbutt, N. C.,. .. Zalcberg, J. R. (2008). K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med, 359*(17), 1757-1765. doi:10.1056/NEJMoa0804385

Lapeyrere, N., Mathoulin-Pelissier, S., Merlio, J. P., Rullier, A., Belleannee, G., LeBail, B.,. .. Soubeyran, I. (2012). [KRAS analysis management: Process and delays]. *Ann Pathol, 32*(2), 81-90. doi:10.1016/j.annpat.2012.02.001

Leary, A. F., Castro, D. G., Nicholson, A. G., Ashley, S., Wotherspoon, A., O'Brien, M. E., & Popat, S. (2012). Establishing an EGFR mutation screening service for non-small cell lung cancer - sample quality criteria and candidate histological predictors. *Eur J Cancer, 48*(1), 61-67. doi:10.1016/j.ejca.2011.09.022

Lievre, A., Artru, P., Guiu, M., Laurent-Puig, P., Merlin, J. L., Sabourin, J. C.,. .. Ducreux, M. (2013). The KRAS mutation detection within the initial management of patients with metastatic colorectal cancer: a status report in France in 2011. *Eur J Cancer, 49*(9), 2126-2133. doi:10.1016/j.ejca.2013.02.016

Lim, C., Tsao, M. S., Le, L. W., Shepherd, F. A., Feld, R., Burkes, R. L.,. .. Leighl, N. B. (2015). Biomarker testing and time to treatment decision in patients with advanced nonsmall-cell lung cancer. *Ann Oncol, 26*(7), 1415-1421. doi:10.1093/annonc/mdv208

Lim, S. J., Cantillep, A., & Carpenter, P. M. (2013). Validation and workflow optimization of human epidermal growth factor receptor 2 testing using INFORM HER2 dual-color in situ hybridization. *Hum Pathol, 44*(11), 2590-2596. doi:10.1016/j.humpath.2013.07.005

Lindeman, N. I., Cagle, P. T., Beasley, M. B., Chitale, D. A., Dacic, S., Giaccone, G.,. .. Ladanyi, M. (2013). Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. *J Thorac Oncol, 8*(7), 823-859. doi:10.1097/JTO.0b013e318290868f

Lowe, K., Kelsh, M. A., McCarl, K., & Bohac, G. C. (2016). *Characterization of KRAS, NRAS, and BRAF testing and timing among mCRC patients treated at community cancer centers in the United States.* Paper presented at the ASCO Annual Meeting Proceedings.

Madrid, M. A., & Lo, R. W. (2004). Chromogenic in situ hybridization (CISH): a novel alternative in screening archival breast cancer tissue samples for HER-2/neu status. *Breast Cancer Res, 6*(5), R593-600. doi:10.1186/bcr915

McDonald, S. A., Watson, M. A., Rossi, J., Becker, C. M., Jaques, D. P., & Pfeifer, J. D. (2011). A new paradigm for biospecimen banking in the personalized medicine era. *Am J Clin Pathol, 136*(5), 679-684. doi:10.1309/ajcp7dwcq1swjtwu

Melchior, L., Grauslund, M., Bellosillo, B., Montagut, C., Torres, E., Moragon, E.,. .. Jans, C. (2015). Multi-center evaluation of the novel fully-automated PCR-based Idylla BRAF Mutation Test on formalin-fixed paraffin-embedded tissue of malignant melanoma. *Exp Mol Pathol, 99*(3), 485-491. doi:10.1016/j.yexmp.2015.09.004

Morgan, S., Donald, E., Ryan, A., Kockx, M., Verstrepen, W., & Tepperberg, J. (2011). *Evaluation of non-small cell lung cancer (NSCLC) tumour sample requirements for EGFR and KRAS mutation analysis.* Paper presented at the ANNALS OF ONCOLOGY.

Morris, V. K., Overman, M. J., Kee, B. K., Fogelman, D. R., Eng, C., Dasari, A.,. .. Garrett, C. R. (2014). *Efficiency of biomarker screening for enriched metastatic colorectal cancer trials: The ATTACC program experience.* Paper presented at the ASCO Annual Meeting Proceedings.

NICE. (2015). *Multiple Technology Appraisal: Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer ID794 (Committee papers)*. Retrieved from https://www.nice.org.uk/guidance/GID-TAG470/documents/committee-papers

Peeters, M., Oliner, K., Parker, A., Huang, J., Siena, S., Humblet, Y.,. .. Reese, D. (2010). *Use of massively parallel, next-generation sequencing to identify gene mutations beyond KRAS that predict response to panitumumab in a randomized, phase 3, monotherapy study of metastatic colorectal cancer (mCRC).* Paper presented at the 2010 American Association for Cancer Research 101st Annual Meeting, Washington, DC, USA.

Penault-Llorca, F., Abrial, C., Mouret-Reynier, M. A., Raoelfils, I., Durando, X., Leheurteur, M.,. .. Chollet, P. (2007). Achieving higher pathological complete response rates in HER-2-positive patients with induction chemotherapy without trastuzumab in operable breast cancer. *Oncologist, 12*(4), 390-396. doi:10.1634/theoncologist.12-4-390

Raetskaya-Solntseva, O., & Laudadio, J. (2012). *Process Improvement: Impact of a Reflex Testing Policy for EGFR and ALK Mutations on Newly Diagnosed Lung Carcinomas.* Paper presented at the JOURNAL OF MOLECULAR DIAGNOSTICS.

Reddy, S. (2010). *ERCC, TS, RRM1, EGFR, and KRAS biomarker integration into a community-based medical oncology practice.* Paper presented at the ASCO Annual Meeting Proceedings.

Sabourin, J.-C., Lièvre, A., Merlin, J.-L., Ducreux, M., Artru, P., Longin, J.,. .. Laurent-Puig, P. (2015). *Review of the current status of RAS mutation testing in patients with metastatic colorectal cancer (mCRC): Flash-RAS study.* Paper presented at the 18th Annual European Congress of the International Society for Pharmacoeconomics and Outcome Research, ISPOR.

Saini, S. D., Schoenfeld, P., & Vijan, S. (2010). Surveillance colonoscopy is cost-effective for patients with adenomas who are at high risk of colorectal cancer. *Gastroenterology, 138*(7), 2292-2299, 2299.e2291. doi:10.1053/j.gastro.2010.03.004

Schwaederle, M., Parker, B. A., Schwab, R. B., Fanta, P. T., Boles, S. G., Daniels, G. A.,. .. Kurzrock, R. (2014). Molecular tumor board: the University of California-San Diego Moores Cancer Center experience. *Oncologist, 19*(6), 631-636. doi:10.1634/theoncologist.2013-0405

Scott, R. J., Fox, S. B., Desai, J., Grieu, F., Amanuel, B., Garrett, K.,. .. Iacopetta, B. (2014). KRAS mutation testing of metastatic colorectal cancer in Australia: where are we at? *Asia Pac J Clin Oncol, 10*(3), 261-265. doi:10.1111/ajco.12201

Shaaban, A. M., Purdie, C. A., Bartlett, J. M., Stein, R. C., Lane, S., Francis, A.,. .. Pinder, S. E. (2014). HER2 testing for breast carcinoma: recommendations for rapid diagnostic pathways in clinical practice. *J Clin Pathol, 67*(2), 161-167. doi:10.1136/jclinpath-2013-201819

Smith, B. L., Breitfeld, P., Cubino, J., Weigman, V., Richards, D. P., & Chung, K. Y. (2014). Feasibility study of genomic biomarker profiling for patients with metastatic colorectal cancer. *Cancer Research, 74*(19 Supplement), 5187-5187.

Spigel, D., Ervin, T., Ramlau, R., Daniel, D., Goldschmidt, J., Krzakowski, M.,. .. Peterson, A. (2010). *Randomized multicenter double-blind placebo-controlled phase II study evaluating MetMAb, an antibody to Met receptor, in combination with erlotinib, in patients with advanced non-small-cell lung cancer.* Paper presented at the Annals of Oncology.

Takahashi, H., Shitara, K., Kuwata, T., Naito, Y., Matsumoto, S., Okamoto, W.,. .. Yamada, Y. (2013). Abstract B29: Feasibility of amplicon sequencing using a pan-cancer gene panel with pre-treatment biopsy samples of (Japanese) patients with advanced solid tumors: Analyses of Biopsy Samples for Cancer Genomics (ABC) study. *Molecular Cancer Therapeutics, 12*(11 Supplement), B29-B29.

Toulmonde, m., grellety, t., auzanneau, c., laizet, y. h., tran, k., floquet, a.,. .. soubeyran, i. (2015). Abstract C48: BIP (Bergonie Institute profiling) program: Fighting cancer by matching molecular alterations and drugs in early phase trials. *Molecular Cancer Therapeutics, 14*(12 Supplement 2), C48-C48.

Tran, B., Dancey, J. E., Bedard, P. L., Kamel-Reid, S., McPherson, J. D., Stein, L. D.,. .. Ferretti, V. (2011). Abstract B48: Feasibility study of molecular profiling (MP) in patients (Pts) with advanced solid cancers using targeted mutation analysis and targeted exome sequencing. *Molecular Cancer Therapeutics, 10*(11 Supplement), B48-B48.

Tsao, M., Ionescu, D., Chong, G., Magliocco, A., Soulieres, D., Hwang, D.,. .. Karsan, A. (2011). *Population-based pan-Canadian EGFR-mutation testing program.* Paper presented at the ASCO Annual Meeting Proceedings.

Tumer, S., Steinmetz, H., Dinulos, M., Moeschler, J., Vallee, S., Upton, S.,. .. Church, D. (2014). *The Clinical Utility of Clinical Whole Exome Sequencing.* Paper presented at the JOURNAL OF MOLECULAR DIAGNOSTICS.

Van Cutsem, E., Lang, I., D'Haens, G., Moiseyenko, V., Zaluski, J., Folprecht, G.,. .. Rougier, P. (2008). *KRAS status and efficacy in the CRYSTAL study: 1st-line treatment of patients with metastatic colorectal cancer (mCRC) receiving FOLFIRI with or without cetuximab.* Paper presented at the Annals of oncology.

van Krieken, J. H., Siebers, A. G., & Normanno, N. (2013). European consensus conference for external quality assessment in molecular pathology. *Ann Oncol, 24*(8), 1958-1963. doi:10.1093/annonc/mdt153

Wagle, N., Van Allen, E., Perrin, D., Friedrich, D., Fisher, S., Kryukov, G.,. .. Joffe, S. (2013). CanSeq: prospective clinical whole-exome sequencing of FFPE tumor samples. *Cancer Research, 73*(8 Supplement), 3152-3152.

Walther, Z., Ronski, K., Wan, M., & Sklar, J. (2012). *A TaqMan array system for mutation profiling of solid tumors using routine surgical pathology and cytology specimens.* Paper presented at the JOURNAL OF MOLECULAR DIAGNOSTICS.

Wu, H. H., Randolph, M., Post, K. M., Sen, J. D., Malek, A. J., & Cheng, L. (2014). Utilization of tumor cell enriched cell transfer technique in detection of EGFR and KRAS mutation on small biopsies of patients with diagnoses of adenocarcinoma. *Laboratory Investigation, 94*, 532A.

Yardley, D., Burris, H., Chandra, P., Liang, S., Ma, Z., Shastry, M., & Hainsworth, J. (2013). Abstract PD4-3: Use of community-based next-generation sequencing (NGS) in advanced breast cancer: Identification of actionable targets to guide clinical trial selection. *Cancer Research, 73*(24 Supplement), PD4-3-PD4-3.