# MSAC Application 1172:

# Final Decision Analytical Protocol (DAP) to guide the assessment of BRAF genetic testing in patients with melanoma for access to proposed PBS- funded vemurafenib

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## MSAC and PASC

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

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

## Purpose of this document

This document is intended to provide a decision analytical protocol (DAP) that will be used to guide the assessment of BRAF genetic testing in melanoma. The protocol has been finalised after inviting relevant stakeholders to provide input. This protocol will provide the basis for the assessment of the intervention. PASC noted that other matters were raised in the public and stakeholder feedback and the response from the applicant, but judged that addressing these would not substantially alter the final DAP.

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

> **P**atients – specification of the characteristics of the patients or population in whom the intervention is to be considered for use;
> **I**ntervention – specification of the proposed intervention;
> **C**omparator – specification of the therapy most likely to be replaced by, or used in addition with, the proposed intervention; and
> **O**utcomes – specification of the health outcomes and the healthcare resources likely to be affected by the introduction of the proposed intervention.

## Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of BRAF V600 testing for unresectable IIIC or metastatic stage IV cutaneous melanoma was received from Roche Diagnostics Australia Pty Limited and Roche Products Pty Limited (Australia) by the Department of Health and Ageing in June 2011. The proposal relates to a new test that is currently not available on the MBS.

Adelaide Health Technology Assessment (AHTA), School of Population Health and Clinical Practice, University of Adelaide, as part of its contract with the Department of Health and Ageing, drafted an earlier version of this DAP to guide the assessment of the safety, effectiveness and cost-effectiveness of BRAF genetic testing in order to inform MSAC's decision-making regarding public funding of the intervention.

## Background

### Current arrangements for public reimbursement

Currently, BRAF genetic testing is not eligible for reimbursement under Medicare. However, a small number of laboratories in Australia do offer the service for a fee.

According to the Royal College of Pathologists of Australasia (2011), four laboratories in Australia offer BRAF testing – the Department of Neuropathology, Royal Prince Alfred Hospital, NSW; Hunter Area Pathology Service, John Hunter Hospital; Hunter New England Health, NSW; Molecular Pathology, Gribbles Pathology, VIC; and Molecular Pathology, SA Pathology, SA (Royal College of Pathologists of Australasia 2011). Additional laboratories may also provide testing in a research and/or clinical setting.

The application for BRAF V600 testing has been submitted as part of an assessment for a co-dependent technology where testing would identify the subpopulation of patients with unresectable stage IIIC or metastatic stage IV cutaneous melanoma who are likely to respond to vemurafenib. However, vemurafenib is currently not under evaluation by the Pharmaceutical Benefits Advisory Committee (PBAC) and is yet to receive Therapeutic Goods Administration (TGA) approval for use in Australia.

There are no Medicare data available regarding the likely utilisation of BRAF genetic testing. In 2007, the age-standardised incidence of melanoma of the skin was 57.2

per 100 000 males and 38.2 per 100 000 females although the incidence of newly diagnosed unresectable or metastatic cases of melanoma is only a small proportion of this total number of cases.

Cutaneous melanoma can be staged using the TNM staging criteria. The American Joint Committee on Cancer (AJCC) has published a revised staging system which suggests that patients with stage IIIC or IV melanoma have pathological evidence of at least one nodal macrometastasis or distant metastases (American Joint Committee on Cancer 2010). Table 1 and Table 2 define the different stages in melanoma of the skin with the blue shading indicating those staging group criteria which would be required for BRAF genetic testing, if testing is undertaken in accordance with the applicant's request.

According to cancer registry data in NSW, the proportion of incident cases of melanoma which are localised (AJCC[1] stage I and II), regional (AJCC stage III) or distant (AJCC stage IV) are 84%, 7.7%, and 4.6% respectively. Approximately 4% of incident cases are of an unknown stage (NSW Central Cancer Registry 2011).

[1] American Joint Committee on Cancer (AJCC)

Table 1 TNM staging categories for cutaneous melanoma

| T stage | Thickness (mm) | Ulceration status/mitoses |
|---|---|---|
| Tis | N/A | N/A |
| T1 | ≤ 1.00 | a: without ulceration and mitosis < 1/mm$^2$<br>b: with ulceration or mitosis ≥ 1/mm$^2$ |
| T2 | 1.01–2.00 | a: without ulceration<br>b: with ulceration |
| T3 | 2.01–4.00 | a: without ulceration<br>b: with ulceration |
| T4 | > 4.00 | a: without ulceration<br>b: with ulceration |
| **N stage** | **No of metastatic nodes** | **Nodal metastatic burden** |
| N0 | 0 | N/A |
| N1 | 1 | a: micrometastasis[1]<br>b: macrometastasis[2] |
| N2 | 2–3 | a: micrometastasis[1]<br>b: macrometastasis[2]<br>c: in transit metastases / satellites without metastatic nodes |
| N3 | Pathologic: 4+ metastatic nodes, or matted nodes, or in transit metastases / satellites with metastatic nodes<br>Clinical: ≥ 1 node with in transit metastases / satellite(s) | |
| **M stage** | **Site** | **Serum LDH** |
| M0 | No distant metastases | N/A |
| M1a | Distant skin, subcutaneous, or nodal metastases | Normal |
| M1b | Lung metastases | Normal |
| M1c | All other visceral metastases | Normal |
| | Any distant metastasis | Elevated |

Source: (American Joint Committee on Cancer 2010; Balch et al. 2009); N/A = not applicable; LDH = lactate dehydrogenase.

[1] = micrometastases are diagnosed after sentinel lymph node biopsy

[2] = macrometastases are defined as clinically detectable nodal metastases confirmed pathologically.

Table 2 Anatomic stage groupings for cutaneous melanoma

| Clinical staging[1] | | | | Pathologic staging[2] | | | |
|---|---|---|---|---|---|---|---|
| | T | N | M | | T | N | M |
| 0 | Tis | N0 | M0 | 0 | Tis | N0 | M0 |
| IA | T1a | N0 | M0 | IA | T1a | N0 | M0 |
| IB | T1b | N0 | M0 | IB | T1b | N0 | M0 |
| | T2a | N0 | M0 | | T2a | N0 | N0 |
| IIA | T2b | N0 | M0 | IIA | T2b | N0 | M0 |
| | T3a | N0 | M0 | | T3a | N0 | M0 |
| IIB | T3b | N0 | M0 | IIB | T3b | N0 | M0 |
| | T4a | N0 | M0 | | T4a | N0 | M0 |
| IIC | T4b | N0 | M0 | IIC | T4b | N0 | M0 |
| III | Any T | N > N1 | M0 | IIIA | T1-4a | N1a | M0 |
| | | | | | T1-4a | N2a | M0 |
| | | | | IIIB | T1-4b | N1a | M0 |
| | | | | | T1-4b | N2a | M0 |
| | | | | | T1-4a | N1b | M0 |
| | | | | | T1-4a | N2b | M0 |
| | | | | | T1-4a | N2c | M0 |
| | | | | IIIC | T1-4b | N1b | M0 |
| | | | | | T1-4b | N2b | M0 |
| | | | | | T1-4b | N2c | M0 |
| | | | | | Any T | N3 | M0 |
| IV | Any T | Any N | M1 | IV | Any T | Any N | M1 |

Source: (American Joint Committee on Cancer 2010)

[1] Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

[2] Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial (ie sentinel node biopsy) or complete lymphadenectomy. Pathologic stage 0 or stage IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.

The incidence rate of melanoma of the skin has increased in both males and females since 1982. For males, the incidence rate more than doubled over a 26-year period from 27 cases per 100 000 males in 1982 to 57 cases per 100 000 males in 2007. The rate for females increased by 47% from 26 cases per 100 000 females in 1982 to 38 cases per 100 000 females in 2007 (AIHW & AACR 2010). Mortality from melanoma of the skin in 2007 was 1 279 and is estimated to have been 1 500 in 2010 (AIHW & AACR 2010).

## Regulatory status

In vitro diagnostic medical devices (IVDs) are pathology tests and related instrumentation used to carry out testing on human samples, where the results are intended to assist in clinical diagnosis or in making decisions concerning clinical management (Therapeutic Goods Administration 2009).

The TGA regulatory framework for IVDs changed in July 2010, such that all IVDs now require premarket approval by the TGA (unless they were offered prior to July 1, 2010 in Australia whereby a transition period up to 2014 applies). As testing for BRAF mutations is currently only provided as an in-house IVD, it would be classified as a Class 3 in-house IVD (see Box 1). Any commercially available BRAF testing kits for the purposes of guiding therapy would, similarly, be classified as Class 3 IVDs.

Laboratories that manufacture in-house Class 3 IVDs are required to notify the TGA of the types of IVDs manufactured in each laboratory for inclusion on a register. These laboratories must have National Association of Testing Authorities (NATA) accreditation, with demonstrated compliance with the suite of standards on the validation of in-house IVDs, as published by the National Pathology Accreditation Advisory Committee (NPAAC), for each test manufactured. The laboratory itself must meet the standard published by the International Organization for Standardization known as ISO 15189, Medical laboratories — Particular requirements for quality and competence.[2] Commercially available Class 3 IVDs must hold certification from a regulatory body to show compliance with a suitable conformity assessment procedure (Therapeutic Goods Administration 2010; Therapeutic Goods Administration 2011).

Roche Diagnostics Australia Pty Ltd is in the process of gaining TGA approval for the COBAS 4800 BRAF V600 mutation test. The Applicant has indicated that no other commercial BRAF mutation tests have received Australian regulatory approval or have approval pending. Other in-house IVDs may also have been developed and be in use for BRAF testing; however, since laboratory developed assays are not required to be entered on the Australian Register of Therapeutic Goods (ARTG) until 2014, their existence and supply is largely unknown.

[2] Therapeutic Goods (Medical Devices) Amendment Regulations 2010 (No. 1) - F2010L00469. Available at: http://www.comlaw.gov.au/Details/F2010L00469

Box 1 Classification of Class 3 In Vitro Diagnostic (IVD) medical devices

Therapeutic Goods (Medical Devices) Regulations 2002 –Schedule 2A

1.3 Detection of transmissible agents or biological characteristics posing a moderate public health risk or high personal risk

1. An IVD is classified as Class 3 IVD medical devices or a Class 3 in-house IVD if it is intended for any of the following uses:
    a. detecting the presence of, or exposure to, a sexually transmitted agent;
    b. detecting the presence in cerebrospinal fluid or blood of an infectious agent with a risk of limited propagation;
    c. detecting the presence of an infectious agent where there is a significant risk that an erroneous result would cause death or severe disability to the individual or foetus being tested;
    d. pre-natal screening of women in order to determine their immune status towards transmissible agents;
    e. determining infective disease status or immune status where there is a risk that an erroneous result will lead to a patient management decision resulting in an imminent life-threatening situation for the patient;
    f. the selection of patients for selective therapy and management, or for disease staging, or in the diagnosis of cancer;
    g. human genetic testing;
    h. to monitor levels of medicines, substances or biological components, when there is a risk that an erroneous result will lead to a patient management decision resulting in an immediate life-threatening situation for the patient;
    i. the management of patients suffering from a life-threatening infectious disease;
    j. screening for congenital disorders in the foetus.

Note: For paragraph (f) An IVD medical device would fall into Class 2 under clause 1.5 if:

    k. a therapy decisions would usually be made only after further investigation; or
    l. the device is used for monitoring.

2. Despite subsection (1) an IVD is classified as a Class 3 IVD medical device or a Class 3 in-house IVD if it is used to test for transmissible agents included in the Australian National Notifiable Diseases Surveillance System (NNDSS) list as published from time to time by the Australian government.

Source: http://www.tga.gov.au/industry/ivd-framework-overview.htm [accessed 2nd August 2011]

# Intervention

## Description

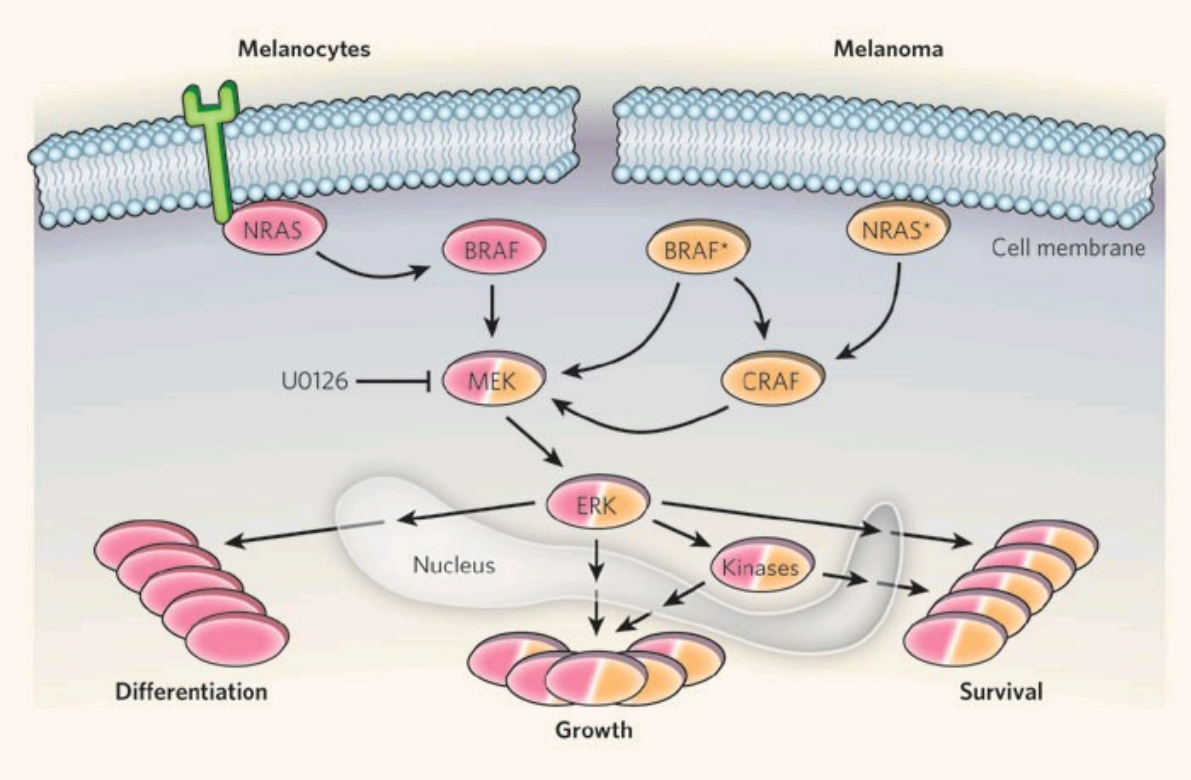
Mutations of the BRAF protein kinase gene are the most common mutations leading to human cancers (Bollag et al. 2010). Specifically in metastatic melanoma, the V600 mutation occurs in approximately 50% of cases, with some evidence that the mutation is associated with a significantly shorter duration of response to standard therapy compared to patients with no BRAF mutation. Of all reported BRAF mutations, the majority involve a single-base missense mutation which results in an amino acid substitution of glutamic acid for valine (V600E mutation). This mutation leads to substantially increased kinase activity and subsequent extracellular signal-

regulated kinase signalling and increased cellular proliferation (Chapman et al. 2011; Kumar et al. 2003; Puzanov & Flaherty 2010).

Metastatic melanoma is associated with a median survival of 6–10 months with little clinical benefit gained from current systemic chemotherapies or immunotherapy in the majority of patients (Shepherd, Puzanov & Sosman 2010).

Vemurafenib is a new BRAF kinase inhibitor which targets the mutated BRAF enzyme and inhibits the activation of the MAPK pathway (Figure 1). The anti-tumour effects of vemurafenib that are seen in BRAF mutated melanoma cell lines are not replicated in cells with a wild-type (normal) BRAF gene (Chapman et al. 2011).

Figure 1 Genetic lesions in melanoma – targeting BRAF gain of function mutations.




In healthy melanocytes, the NRAS-BRAF-MEK-ERK signalling cascade (pink) tightly regulates cellular functions such as differentiation, growth and survival. In melanoma (orange), BRAF mutations (BRAF*) bypass activation by NRAS, leading to cancer-associated signalling through the MEK-ERK pathway that favours growth and survival over differentiation. BRAF* can also activate this pathway through direct activation of CRAF. Mutant NRAS (NRAS*), however, activates MEK-ERK independently of BRAF, through CRAF (Huang & Marais 2009).

**Source: (Huang & Marais 2009)**

Selecting patients who would likely gain clinical benefit from vemurafenib requires detection of a V600E or V600K mutation in the BRAF gene (Chapman et al. 2011). There are several different methodologies that can be used to detect these

mutations, with assays developed in-house including Sanger sequencing, 454 sequencing, allele-specific polymerase chain reaction (PCR), amplification refractory mutation system (ARMS), or ligase detection reaction.

Alternatively, regulatory approval by the TGA is currently being sought for the COBAS 4800 BRAF V600 mutation test, which is a trademarked real time PCR molecular diagnostic test, developed by Roche Diagnostics Pty Ltd, which identifies the V600E mutation (and has cross-reactivity with the V600K mutation) and was used to identify eligible patients in the key evidence (Chapman et al. 2011) supporting this application for MBS funding.

## Delivery of the intervention

PASC advises that the tested population and definition of biomarker in the key trial/s supporting an application should be presented as a scenario in the decision analysis describing the clinical place of a proposed biomarker-drug co-dependent technology alongside other scenarios examining the applicability of the evidence to related clinical practice options.

The tested population in the BRIM-3 trial (Chapman et al. 2011) was previously untreated patients with unresectable stage IIIC or metastatic stage IV melanoma. Those that tested positive for a BRAF V600E (or V600K[3]) mutation using the COBAS 4800 BRAF V600 test were considered eligible for vemurafenib therapy.

Alternative scenarios to be examined in the decision analysis include (see also Table 4):

1. for the tested population:

    - also testing patients with unresectable stage IIIA disease, stage IIIB disease and resectable stage IIIC disease (the base case for the decision analysis), on the expectation that this reflects a greater than 50% likelihood that these patients will progress to disease for which vemurafenib would be eligible if test positive

[3] The trial protocol (http://www.roche-trials.com/trialDetailsGet.action?studyNumber=NO25026) stated that positivity for a BRAF V600E mutation using the COBAS 4800 BRAF V600 test was an eligibility criterion but it was later found – when samples were re-tested using a reference standard of Sanger ± 454 sequencing - that the COBAS test had a 66% (25/38) cross-reactivity for BRAF V600K mutations

- also testing patients with resectable stage IIIA disease (ie testing all patients with stage III and IV disease), noting that this adds a group of patients with a lower likelihood of progressing

- testing all patients with unresectable stage III or metastatic stage IV melanoma, to enable a comparison with the population tested in the trial for the competing GSK2118436 BRAF inhibitor

2. for the biomarker (where BRAF biomarker positive as detecting V600E or V600K is the base case for the decision analysis, reflecting the claim that V600K also predicts variation in the treatment effect of vemurafenib):

- defining BRAF biomarker positive as detecting V600E only, which restricts the definition to the V600 mutation primarily examined in the trial evidence generated for vemurafenib

- defining BRAF biomarker positive as detecting a V600 mutation without further qualification, which adds a small proportion of V600 mutations which might also predict variation in the treatment effect of vermurafenib.

BRAF genetic testing is likely to require retrieval of archival formalin-fixed tissue blocks of the primary cutaneous melanoma which would then undergo mutation testing. It is possible that testing of a specimen (eg fine needle aspirate) from a more recent metastatic tumour might also occur, although it should be noted that the COBAS 4800 BRAF V600 mutation test has only been validated on formalin fixed paraffin embedded tissue specimens[4].

There are few available data regarding the incidence or prevalence of unresectable or metastatic melanoma; therefore, it is difficult to determine the likely number of patients that would be eligible for BRAF testing. The Applicant has estimated that 1 624 patients per year with unresectable or metastatic melanoma would be eligible for testing in 2013. This estimate is based on an assumption that the mortality rate from melanoma is a good predictor of the number of patients with metastatic or unresectable disease, which is a reasonable argument given the median survival of this population is less than one year. PASC estimated that approximately 10% of these patients would not undergo testing as they would not be suitable candidates

[4] US Package Insert for COBAS BRAF test – available at http://www.accessdata.fda.gov/cdrh_docs/pdf11/P110020c.pdf

to receive vemurafenib due to their poor performance status. Therefore, it is estimated that in 2013, 1 462 patients would undergo BRAF testing.

The majority of patients would require testing for BRAF mutations only once; although there may be circumstances where repeat testing would occur after an inconclusive result. The rate of repeat testing may vary according to many factors such as the analytic sensitivity limits of detection for each BRAF testing method, the number of mutant sequence copies present in a specimen, specimen integrity, the amount of isolated DNA, and the presence of interfering substances (eg melanin).

## Prerequisites

Usually, a general practitioner, dermatologist or surgeon would be responsible for taking a biopsy sample of the primary cutaneous lesion. A medical oncologist would order BRAF genetic testing when determining treatment options. High levels of melanin in Tumour tissue may affect testing results.

As noted above, clinical practice may vary with respect to the timing of BRAF testing of a melanoma sample. Testing could be undertaken when a diagnosis of unresectable stage IIIC or metastatic stage IV cutaneous melanoma is made (equivalent to the trial population), to immediately inform vemurafenib eligibility. Equally, testing could occur at melanoma diagnosis (regardless of initial staging) and be used for treatment planning, even though vemurafenib eligibility would still only activate once the patient had progressed to unresectable stage IIIC or metastatic stage IV melanoma. The implication of earlier testing is that for a large proportion of patients the test results would not be needed because the patient would never be eligible for vemurafenib treatment; alternatively, earlier testing would reduce the need for tissue retrieval at a later date – so treatment can commence immediately - and lessen the impact of tissue storage methods (eg formalin fixation) on the DNA in the tumour material and thus the accuracy of BRAF testing.[5]

Given that NATA accreditation would be required by laboratories to provide this service using in-house BRAF tests, it is unlikely that there would be issues regarding access to the required equipment. The tissue sample for analysis would be selected by an anatomical pathologist and macro-dissected or micro-dissected as required.

[5] As noted earlier, the COBAS 4800 BRAF V600 mutation test has only been validated on formalin fixed paraffin embedded tissue specimens.

Competence to perform the test would need to be monitored through the Royal College of Pathologists of Australasia (RCPA) quality assurance programme (QAP). A pilot QAP for BRAF V600 testing was introduced in late 2010 and the first round is currently being evaluated, although it is unclear when the results of this evaluation will be made available.

It is unlikely that laboratories accredited to provide this service would be located in rural or remote areas. Consequently, it would be anticipated that tissue biopsies or specimens would need to be sent to accredited laboratories in metropolitan areas or large regional laboratories.

### Co-administered and associated interventions

BRAF genetic testing is a co-dependent technology with the purpose of identifying patients, with unresectable stage IIIC or metastatic stage IV cutaneous melanoma, who are likely to benefit from treatment with vemurafenib. Such patients who have a biopsy sample which has tested positive for a BRAF V600E or V600K mutation would receive the recommended dose of vemurafenib (960 mg twice daily) orally, until disease progression or until unacceptable toxicity develops.

## Listing proposed and options for MSAC consideration

### Proposed MBS listing

Details of the proposed MBS listing, reflecting the 'base case' use of BRAF genetic testing for access to PBS-funded vemurafenib, are shown in Table 3. However, given there is uncertainty regarding the most cost-effective use of BRAF testing to target vemurafenib therapy in patients with melanoma, several scenarios will need to be explored in any assessment of BRAF genetic testing (Table 4) to be submitted to MSAC.

Table 3 Proposed MBS item descriptor for BRAF genetic testing in metastatic melanoma

| Category 6 – Pathology Services |
| --- |
| MBS [**proposed MBS item**]<br>A test of tumour tissue from a patient with unresectable stage IIIA or stage IIIB or stage IIIC or metastatic stage IV cutaneous melanoma to determine if the requirements relating to BRAF gene mutation status for access to vemurafenib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.<br>Fee: $[285–325] |

## Clinical place for proposed intervention

BRAF genetic testing, in addition to usual care, would be used to identify a subgroup of patients who, with unresectable stage IIIC or metastatic stage IV cutaneous melanoma, would likely benefit from treatment with vemurafenib. In the current management of metastatic melanoma without determination of BRAF genetic status, the majority of patients with these stages of disease receive dacarbazine - or less commonly fotemustine - as first-line chemotherapy, with or without a T cell immunostimulant (ie ipilimumab) or fotemustine as a second line treatment.

In the proposed algorithm, all patients with these stages of disease would be treated according to the results of BRAF genetic testing. Those with an eligible mutation would then be eligible to receive vemurafenib, while those who have no evidence of these mutations (and those who fail vemurafenib treatment) would receive dacarbazine or - less commonly - fotemustine chemotherapy. Those who failed these treatments would receive a T cell immunostimulant (ie ipilimumab) or fotemustine as subsequent therapy. Those who were considered unable to tolerate chemotherapy would be eligible for ipilimumab treatment (see Figure 2 which outlines the TGA-approved melanoma treatments).

No Australian guidelines are currently available which recommend the use of BRAF genetic testing in melanoma patients or treatment with vemurafenib. This is consistent with the recent emergence of these co-dependent technologies; however, some clinical guidelines are available which suggest that immunotherapy is a treatment option and that some immunotherapies are currently being studied as adjuvant therapy (National Comprehensive Cancer Network Inc 2010). Further, members of the Medical Expert Standing Panel (MESP) advise that there is the potential for future use of BRAF genetic testing in an adjuvant setting, in patients with high risk primary melanoma[6]. As such, a scenario addressing this patient group could have been included in Table 4 as requiring investigation.

As there is currently no other method of selecting patients with unresectable stage IIIC or metastatic stage IV cutaneous melanoma suitable for treatment with vemurafenib, BRAF genetic testing would satisfy an unmet clinical need. The Applicant proposes that the use of these co-dependent technologies is expected to

[6] Patients with resected AJCC stage IIC, IIB and IIIC disease are at high risk of dying of melanoma (< 50% ten-year survival) and should be considered for adjuvant systemic therapy (Australian Cancer Network Melanoma Guidelines Revision Working Party 2008).

improve overall survival, progression-free survival and response rates in those patients with a BRAF V600E or V600K mutation who are eligible for vemurafenib, based on data from the BRIM-3 trial (Chapman et al. 2011). It should be noted that patients in the BRIM-3 trial were selected for vemurafenib treatment on the basis of a BRAF V600E mutation detected by the COBAS 4800 V600 mutation test, although 20 of the 675 patients were later found to have a non-V600E mutation. 4 of the 10 patients receiving vemurafenib, who were later found to have a V600K mutation, responded to the treatment. Further research is required to formally assess the effectiveness and safety of vemurafenib in patients with a non-V600E mutation.

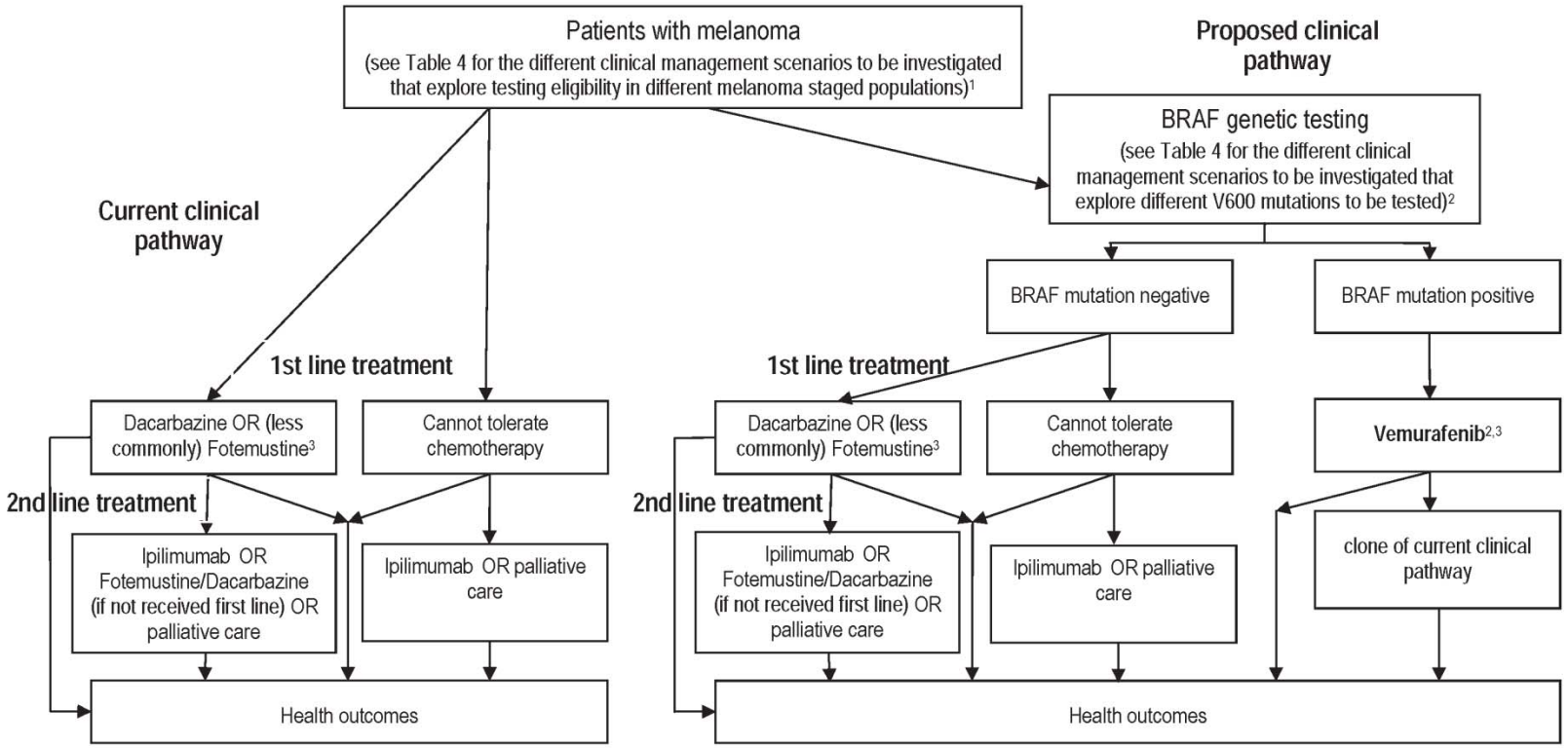
Table 4 Scenarios outlining population eligible for BRAF genetic testing

| Scenarios | Mutation | Staging of cutaneous melanoma |
|---|---|---|
| Trial-based scenario | V600E or V600K | Unresectable stage IIIC or metastatic stage IV |
| Alternative scenario I (mutation broad/same staging) | V600E only[a] | Unresectable stage IIIC or metastatic stage IV |
| Alternative scenario 2 (mutation restrictive/same staging) | any V600[b] | Unresectable stage IIIC or metastatic stage IV |
| Scenario 3a (base case) (trial-based mutation/staging broad) | V600E or V600K | Unresectable stage IIIA or unresectable stage IIIB or unresectable stage IIIC or resectable stage IIIB or resectable stage IIIC or stage IV |
| Alternative scenario 3b (mutation broad/staging broad) | V600E only[a] | Unresectable stage IIIA or unresectable stage IIIB or unresectable stage IIIC or resectable stage IIIB or resectable stage IIIC or stage IV |
| Alternative scenario 3c (mutation restrictive/staging broad) | any V600[b] | Unresectable stage IIIA or unresectable stage IIIB or unresectable stage IIIC or resectable stage IIIB or resectable stage IIIC or stage IV |
| Alternative scenario 4a (trial-based mutation/staged high risk melanoma population) | V600E or V600K | Resectable or unresectable stage IIIA, IIIB, IIIC or IV |
| Alternative scenario 4b (mutation broad/staged high risk melanoma population) | V600E only[a] | Resectable or unresectable stage IIIA, IIIB, IIIC or IV |
| Alternative scenario 4c (mutation restrictive/staged high risk melanoma population) | any V600[b] | Resectable or unresectable stage IIIA, IIIB, IIIC or IV |
| Alternative scenario 5a (trial-based mutation/tested trial population of competing BRAF inhibitor) | V600E or V600K | Unresectable stage IIIA, IIIB, IIIC or IV |
| Alternative scenario 5b (mutation broad/tested trial population of competing BRAF inhibitor) | V600E only[a] | Unresectable stage IIIA, IIIB, IIIC or IV |
| Alternative scenario 5c (mutation restrictive/tested trial population of competing BRAF inhibitor) | any V600[b] | Unresectable stage IIIA, IIIB, IIIC or IV |

[a] ~90% of V600 mutations are V600E; [b] ~50% of metastatic melanoma has a V600 mutation

In addition to the scenarios investigated above, and as part of the assessment of BRAF testing, evidence will need to be provided to confirm that the different V600 mutations are stable, i.e., that once a particular V600 mutation sub-type is identified, it does not change.

**Figure 2 Management algorithm for use of BRAF genetic testing in melanoma**




[1] Watchful waiting or adjuvant systemic therapy would be appropriate for initial clinical management in the scenario pertaining to high risk melanoma. If the tumour recurs then the patient is eligible for first line chemotherapeutic treatment, unless chemotherapy cannot be tolerated.

[2] Testing will occur on biopsies from primary cutaneous tumour or on specimens (eg fine needle aspiration) from metastatic tumour. Repeat testing or re-biopsying may be required if there is insufficient tumour material to provide a definitive result.

[3] Emerging therapies (eg selective BRAF inhibitor GSK2118436 in combination with MEK inhibitor GSK1120212; or vemurafenib plus ipilimumab) are currently undergoing clinical trials.

## Comparator

The comparator for this assessment is usual care, without testing to determine BRAF genetic status. Consequently the majority of melanoma patients in the comparator arm, regardless of their BRAF mutation status, would receive standard chemotherapy (dacarbazine - or less commonly - fotemustine) as a first-line treatment. Those who failed this treatment would receive a T cell immunostimulant (ie ipilimumab) or fotemustine as second-line therapy. Those who are considered unable to tolerate chemotherapy would be eligible for ipilimumab treatment.

There are no MBS item descriptors for usual care without testing to determine BRAF mutation status. There are MBS items which cover the provision of chemotherapy, although these would also be relevant to the proposed intervention arm.

In addition to the test/treatment strategy defined as the comparator, the test used in the key trial/s supporting an application should constitute an "evidentiary standard" against which other BRAF genetic test options are compared. In the case of BRAF genetic testing to access vemurafenib therapy, the evidentiary standard is the COBAS 4800 BRAF V600 test.

## Outcomes for safety and effectiveness evaluation

The health outcomes, upon which the comparative clinical performance of BRAF testing versus the comparator of usual care with no BRAF testing will be measured, are:

### Effectiveness

Overall survival; quality of life; progression-free survival; response rate (complete response or partial response according to RECIST[7] criteria); duration of response; rate of stable disease; rate of disease progression; time to progression.

### Safety

Psychological and physical harms from testing; any change in adverse events related to different treatments including tolerability, toxicity, neutropenia, QT prolongation,

[7] RECIST = Response Evaluation Criteria in Solid Tumours

rash and additional cancers ; rate of repeat testing; biopsy or fine needle aspiration (FNA) sampling rate.

## Summary of PICO to be used for assessment of evidence (systematic review)

Table 5 provides a summary of the PICO used to:

(1) define the question for public funding,

(2) select the evidence to assess the safety and effectiveness of BRAF genetic testing with vemurafenib in patients with melanoma, and

(3) provide the evidence-based inputs for any decision-analytical modelling to determine the cost-effectiveness of BRAF genetic testing with vemurafenib in patients with melanoma.

Table 5 Summary of PICO to define research questions that assessment will investigate

| Patients | Intervention | Comparator | "Evidentiary" standard | Outcomes to be assessed |
|---|---|---|---|---|
| Patients with cutaneous melanoma<br><br>Staging subgroups for examination of BRAF genetic testing in scenario analyses:<br>• Unresectable stage IIIC or stage IV[a]<br>• Resectable stage IIIB, IIIC or unresectable stage IIIA, IIIB, IIIC or stage IV[b]<br>• Resectable or unresectable stage IIIA, IIIB, IIIC or stage IV[b]<br>• Unresectable stage IIIA, IIIB, IIIC or stage IV[b] | BRAF genetic testing and use of vemurafenib in unresectable stage IIIC or metastatic stage IV[a] patients with a specified BRAF mutation (see below) or current usual care* in patients without these mutations<br><br>Definition of BRAF mutation for examination in scenario analyses:<br>• V600E or V600K<br>• V600E only<br>• any V600<br><br>*Current usual care is defined as dacarbazine or fotemustine as first line treatment ± ipilimumab or fotemustine/ dacarbazine as a second line treatment. Those who are considered unable to tolerate chemotherapy would be eligible for ipilimumab treatment. | No BRAF genetic testing and current usual care*<br><br>*Current usual care is defined as dacarbazine or fotemustine as first line treatment ± ipilimumab or fotemustine/ dacarbazine as a second line treatment. Those who are considered unable to tolerate chemotherapy would be eligible for ipilimumab treatment. | COBAS 4800 BRAF V600 test | **Safety**<br>Psychological and physical harms from testing. Any adverse events related to a change in treatment including tolerability; toxicity; neutropenia; QT prolongation; rash and additional cancers from treatment.<br><br>**Effectiveness[c]**<br>*Direct evidence*<br>Primary outcomes:<br>Overall survival; progression-free survival.<br>Secondary outcomes:<br>Response rate (complete response or partial response according to RECIST criteria); duration of response; rate of stable disease; rate of disease progression; time to progression; quality of life; rate of repeat testing; biopsy or FNA sampling rate.<br><br>**Cost-effectiveness**<br>Cost, cost per relevant health outcome (eg LYG, QALY) |

## Questions

1. Primary (base case) question

Is BRAF genetic testing for V600E or V600K mutations in tumour samples of patients with resectable stage IIIB, IIIC or unresectable stage IIIA, IIIB, IIIC or stage IV cutaneous melanoma, in addition to usual care or targeted treatment with vemurafenib in patients with unresectable stage IIIC or metastatic stage IV cutaneous melanoma, safe, effective and cost-effective compared to usual care alone without BRAF testing?

Secondary questions

2. Is BRAF genetic testing for V600E or V600K mutations in tumour samples, in addition to usual care or targeted treatment with vemurafenib in patients with unresectable stage IIIC or stage IV cutaneous melanoma, safe, effective and cost-effective compared to usual care alone without BRAF testing of patients with:
    - unresectable stage IIIC or stage IV cutaneous melanoma? (trial-based analysis);
    - resectable or unresectable stage IIIA, IIIB, IIIC or stage IV cutaneous melanoma?; or
    - unresectable stage IIIA, IIIB, IIIC or IV stage cutaneous melanoma?
3. Is BRAF genetic testing for V600E mutations only in tumour samples, in addition to usual care or targeted treatment with vemurafenib in patients with unresectable stage IIIC or metastatic stage IV cutaneous melanoma, safe, effective and cost-effective compared to usual care alone without BRAF testing of patients with:
    - unresectable stage IIIC or stage IV cutaneous melanoma?;
    - resectable stage IIIB, IIIC or unresectable stage IIIA, IIIB, IIIC or stage IV cutaneous melanoma?;
    - resectable or unresectable stage IIIA, IIIB, IIIC or stage IV cutaneous melanoma?; or
    - unresectable stage IIIA, IIIB, IIIC or stage IV cutaneous melanoma?
4. Is BRAF genetic testing for any V600 mutation in tumour samples, in addition to usual care or targeted treatment with vemurafenib in patients with unresectable stage IIIC or metastatic stage IV cutaneous melanoma, safe, effective and cost-effective compared to usual care alone without BRAF testing of patients with:
    - unresectable stage IIIC or stage IV cutaneous melanoma?;
    - resectable stage IIIB, IIIC or unresectable stage IIIA, IIIB, IIIC or stage IV cutaneous melanoma?;
    - resectable or unresectable stage IIIA, IIIB, IIIC or stage IV cutaneous melanoma?; or
    - unresectable stage IIIA, IIIB, IIIC or stage IV cutaneous melanoma?

[a] According to the 2009 American Joint Committee on Cancer (American Joint Committee on Cancer 2010)

[b] BRAF genetic testing may occur earlier but patients would only be eligible for treatment with vemurafenib when their staging progresses to unresectable stage IIIC or metastatic stage IV cutaneous melanoma.

[c] Section B of the "Information requests for co-dependent technologies" table (http://health.gov.au/internet/hta/publishing.nsf/Content/co-1) outlines some strategies for linking evidence in the absence of direct trial evidence of the co-dependent package of technologies (ie biomarker/test/drug). In this case this might include systematically reviewing data on the accuracy of BRAF genetic testing – using various testing modalities - relative to the "evidentiary" standard, and linking that to data on observed changes in management associated with BRAF testing, as well as

trial data on the effectiveness of vemurafenib (relative to usual care) in the proposed population. Other important evidence to support the application could include data on the health outcome impact of BRAF genetic testing versus not testing, and the biological rationale for targeting vemurafenib treatment according to the BRAF V600E or V600K biomarker (or potentially other BRAF markers).

N/A = not applicable; RECIST = Response Evaluation Criteria in Solid Tumours; FNA = fine needle aspiration; LYG = life-year gained; QALY = quality adjusted life-year.

## Clinical claim

The Applicant suggests that the intervention will have a significant impact on the treatment of BRAF V600E or V600K mutation-positive melanoma patients. Vemurafenib is suggested to result in a clinically relevant and statistically significant improvement in overall survival, progression-free survival and response rates compared to the main comparator treatment (dacarbazine), in a disease where there are limited treatment options.

There are likely to be different adverse events in BRAF V600E or V600K mutation-positive patients treated with vemurafenib than the comparator; however, the Applicant suggests that the net clinical benefit is expected to outweigh the harms for patients with unresectable stage IIIC or metastatic stage IV cutaneous melanoma.

These claims suggest that BRAF genetic testing, to identify patients who would benefit from vemurafenib, would result in superior health outcomes for individuals found to be BRAF V600E or V600K mutation positive. For those who are found to be mutation negative, the impact of BRAF testing is expected to be negligible as no additional biopsy or invasive testing is expected to be required (noting that BRAF mutations appear to be early persistent mutations in melanoma and so assuming that mutation status between the primary tumour and any metastasis is stable). Relative to the comparator, BRAF testing and treatment with vemurafenib may be considered non-inferior in terms of safety and to be superior in terms of effectiveness. As such, the type of economic evaluation required is a cost-effectiveness analysis or cost-utility analysis (green shading in Table 6). In addition, an exploration of the uncertainty around the estimates of effectiveness and safety should be conducted.

Table 6 Classification of an intervention for determination of economic evaluation to be presented

<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="3">Comparative effectiveness versus comparator</td></tr>
<tr><td colspan="2">Superior</td><td>Non-inferior</td><td colspan="2">Inferior</td></tr>
<tr><td rowspan="7">Comparative safety versus comparator</td><td rowspan="3">Superior</td><td colspan="2" rowspan="3">CEA/CUA</td><td rowspan="3">CEA/CUA</td><td>Net clinical benefit</td><td>CEA/CUA</td></tr>
<tr><td>Neutral benefit</td><td>CEA/CUA*</td></tr>
<tr><td>Net harms</td><td>None^</td></tr>
<tr><td>Non-inferior</td><td colspan="2">CEA/CUA</td><td>CEA/CUA*</td><td colspan="2">None^</td></tr>
<tr><td rowspan="3">Inferior</td><td>Net clinical benefit</td><td>CEA/CUA</td><td rowspan="3">None^</td><td colspan="2" rowspan="3">None^</td></tr>
<tr><td>Neutral benefit</td><td>CEA/CUA*</td></tr>
<tr><td>Net harms</td><td>None^</td></tr>
</table>

Abbreviations: CEA = cost-effectiveness analysis; CUA = cost-utility analysis

* May be reduced to cost-minimisation analysis. Cost-minimisation analysis should only be presented when the proposed service has been indisputably demonstrated to be no worse than its main comparator(s) in terms of both effectiveness and safety, so the difference between the service and the appropriate comparator can be reduced to a comparison of costs. In most cases, there will be some uncertainty around such a conclusion (i.e., the conclusion is often not indisputable). Therefore, when an assessment concludes that an intervention was no worse than a comparator, an assessment of the uncertainty around this conclusion should be provided by presentation of cost-effectiveness and/or cost-utility analyses.

^ No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this intervention

# Outcomes and health care resources affected by introduction of proposed intervention

## Outcomes for economic evaluation

The Applicant claims that there is a statistically significant benefit in terms of overall survival, progression-free survival, and response rates for patients who are eligible for vemurafenib therapy. Therefore, the health outcome for the economic evaluation should be life-years gained or quality-adjusted life-years gained. Additionally, consideration of the comparative safety of BRAF genetic testing and of vemurafenib should be included in the economic evaluation.

## Health care resources

Although there is some question as to whether BRAF genetic testing could occur at the initial diagnostic stage (rather than when the melanoma has progressed so that the patient is eligible for vemurafenib treatment), diagnosis and staging of melanoma will occur in both comparative arms, ie with or without BRAF testing, and

so the costs and resource use associated with these will not be needed in the economic evaluation of BRAF genetic testing.

As the co-dependent drug, vemurafenib, is currently not available in Australia outside of a clinical trial setting, the cost of this drug is an area of uncertainty in the economic evaluation which may require exploration.

Substantial uncertainty remains around the likely number of patients who would undergo BRAF genetic testing in Australia each year. This would require exploration in the economic evaluation unless adequate data are found to inform the question of likely usage. This exploration would need to take the form of investigating the different clinical scenarios outlined in Table 4.

The type of test used to identify the BRAF mutation is also likely to affect the economic evaluation – for example, in terms of the transition probabilities used in the model, particularly the positive predictive value and negative predictive value of the test; and the need for repeat testing or repeated biopsies. The comparative analytical and clinical validity of the different BRAF genetic tests would need to be explored.

Table 7 provides a non-exhaustive list of the resources to be considered in the economic analysis.

**Table 7 List of resources to be considered in the economic analysis**

| | Provider of resource | Setting in which resource is provided | Proportion of patients receiving resource | Number of units of resource per relevant time horizon per patient receiving resource | Disaggregated unit cost | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | MBS | Safety nets* | Other govt budget | Private health insurer | Patient | Total cost |
| Resources provided to deliver BRAF genetic testing – proposed scenario | | | | | | | | | | |
| Block retrieval of stored sample from tissue archive (from most recent biopsy) | Pathologist | | TBD (not all samples will need to be retrieved if biopsy performed at diagnosis of metastatic disease) | 1 | | | | | | TBD |
| Preparation of tissue sample | Pathologist | | 100% | 1 | | | | | | TBD |
| BRAF genetic test | Molecular pathologist | | 100% | 1 | $285–$325 | | | | | $285–$325 |
| Retesting of inconclusive BRAF mutation testing results | Molecular pathologist | | Will differ according to each specific test method used | 1 | $285–$325 | | | | | $285–$325 |
| Resources provided to deliver drug therapy – proposed scenario | | | | | | | | | | |
| Specialist consultation for initiation of vemurafenib (oral) (MBS 110) and regular follow-up (MBS 116) in BRAF mutation positive patients | Medical oncologist | Outpatient | 47% [a] | TBD | MBS 110 $145.20<br>MBS 116 $72.65 | | | | | TBD |
| Vemurafenib | Medical oncologist | Outpatient / inpatient | 47% [a] | 960 mg twice daily orally [b] until disease progression | | | TBD | | | TBD |
| Specialist consultation for initiation of dacarbazine or - less commonly - fotemustine as first-line chemotherapy, with or without a T cell immunostimulant (ie ipilimumab) or dacarbazine/fotemustine (if not used first line) as a second line treatment (MBS 110) and regular follow-up (MBS 116) | Medical oncologist | Outpatient | 53% (BRAF negative patients) | 1<br>TBD | MBS 110 $145.20<br>MBS 116 $72.65 | | | | | $145.20<br>TBD |
| Dacarbazine drug acquisition (first or second line treatment) | Medical oncologist | Day patient | TBD (BRAF negative patients) | TBD | | | $56.41/ vial[c] | | | TBD |

| | Provider of resource | Setting in which resource is provided | Proportion of patients receiving resource | Number of units of resource per relevant time horizon per patient receiving resource | Disaggregated unit cost | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | MBS | Safety nets* | Other govt budget | Private health insurer | Patient | Total cost |
| Fotemustine drug acquisition (first or second line treatment) | Medical oncologist | Day patient | TBD (BRAF negative patients) | TBD | | | $1206.86/vial | | | TBD |
| Ipilimumab drug acquisition (second line treatment) | Medical oncologist | Day patient | TBD (BRAF negative patients) | TBD | | | TBD | | | TBD |
| Drug administration for 1-6 hr infusion (MBS 13918) | Medical oncologist | Day patient | 53% (BRAF negative patients) | TBD | MBS 13918 $94.20 | | | | | TBD |
| Full day hospital admission for chemotherapy administration in a public hospital setting (excluding average pharmacy cost component)[d] | Medical oncologist | Day patient | 53% (BRAF negative patients) weighted by private:public split | TBD | | | $562.00 | | | TBD |
| Full day hospital admission for chemotherapy administration in a private hospital setting (excluding average pharmacy cost component)[e] | Medical oncologist | Day patient | | TBD | | | $331.00 | | | TBD |
| Resources provided in association with proposed intervention – to manage adverse events from vemurafenib – proposed scenario | | | | | | | | | | |
| Dermatologist consultation for suspicious cuSCC lesions (MBS 104; initial) and follow-up (MBS 105) | Dermatologist | Outpatient | 12%[b] | TBD | MBS 104 $82.30<br>MBS 105 $41.35 | | | | | TBD |
| Cutaneous squamous cell carcinoma excision<br>MBS 31280<br>MBS 31285<br>MBS 31290 | Dermatologist | Outpatient | 12%[b] | TBD | <br>$149.95<br>$204.90<br>$236.55 | | | | | TBD |
| Monitoring for QT prolongation, 12 lead electrocardiography (MBS 11700) | Medical oncologist | Outpatient | 47% [a] | TBD | $30.05 | | | | | TBD |
| Resources provided in association with proposed intervention – to manage adverse events from dacarbazine (management of nausea and vomiting) – proposed scenario in BRAF negative patients (with test) | | | | | | | | | | |
| Dexamethasone (IV) (PBS 1291Y) | Medical oncologist | Outpatient / inpatient | 100% | Once before every 3-weekly chemotherapy cycle | | | $27.58 | | | TBD |
| Ondansetron (IV) (PBS 8227B) | Medical | Outpatient / | 100% | Once before every 3- | | | $23.06 | | | TBD |

| | Provider of resource | Setting in which resource is provided | Proportion of patients receiving resource | Number of units of resource per relevant time horizon per patient receiving resource | Disaggregated unit cost | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | MBS | Safety nets* | Other govt budget | Private health insurer | Patient | Total cost |
| | oncologist | inpatient | | weekly chemotherapy cycle | | | | | | |
| Ondansetron (Oral) (PBS 5471Y) | Medical oncologist | Outpatient / inpatient | 100% | For two days after every 3-weekly chemotherapy cycle | | | $37.73 | | | TBD |
| Resources provided to deliver therapy in current scenario | | | | | | | | | | |
| Specialist consultation for initiation of dacarbazine or - less commonly - fotemustine as first-line chemotherapy, with or without a T cell immunostimulant (ie ipilimumab) or dacarbazine/fotemustine (if not used first line) as a second line treatment (MBS 110) and regular follow-up (MBS 116) | Medical oncologist | Outpatient | 100% | 1<br><br><br><br><br>TBD | MBS 110 $145.20<br><br>MBS 116 $72.65 | | | | | $145.20<br><br><br><br><br>TBD |
| Dacarbazine drug acquisition (first or second line treatment) | Medical oncologist | Day patient | TBD | TBD | | | $56.41/ vial[c] | | | TBD |
| Fotemustine drug acquisition (first or second line treatment) | Medical oncologist | Day patient | TBD | TBD | | | $1206.86/vial | | | TBD |
| Ipilimumab drug acquisition (second line treatment) | Medical oncologist | Day patient | TBD | TBD | | | TBD | | | TBD |
| Drug administration for 1-6 hr infusion (MBS 13918) | Medical oncologist | Day patient | 100% | TBD | MBS 13918 $94.20 | | | | | TBD |
| Full day hospital admission for chemotherapy administration in a public hospital setting (excluding average pharmacy cost component)[d] | Medical oncologist | Day patient | 100% weighted by private:public split | TBD | | | $562.00 | | | TBD |
| Full day hospital admission for chemotherapy administration in a private hospital setting (excluding average pharmacy cost component)[e] | Medical oncologist | Day patient | | TBD | | | $331.00 | | | TBD |
| Resources provided in association with current intervention – to manage adverse events from dacarbazine (management of nausea and vomiting) – current scenario in all patients (without test) | | | | | | | | | | |
| Dexamethasone (IV) (PBS 1291Y) | Medical oncologist | Outpatient / inpatient | 100% | Once before every 3-weekly chemotherapy cycle | | | $27.58 | | | TBD |
| Ondansetron (IV) (PBS 8227B) | Medical | Outpatient / | 100% | Once before every 3- | | | $23.06 | | | TBD |

| | Provider of resource | Setting in which resource is provided | Proportion of patients receiving resource | Number of units of resource per relevant time horizon per patient receiving resource | Disaggregated unit cost | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | MBS | Safety nets* | Other govt budget | Private health insurer | Patient | Total cost |
| | oncologist | inpatient | | weekly chemotherapy cycle | | | | | | |
| Ondansetron (Oral) (PBS 5471Y) | Medical oncologist | Outpatient / inpatient | 100% | For two days after every 3-weekly chemotherapy cycle | | | $37.73 | | | TBD |

* Include costs relating to both the standard and extended safety net; TBD = to be determined

[a] BRAF V600E or V600K mutation positive patients; (Chapman et al. 2011)

[b] (Chapman et al. 2011)

[c] Cost provided by Applicant

[d] National Consolidated Cost Weights for AR DRG Version 5.2 - Round 13, 2008-09; Public Sector, Item R63Z – Chemotherapy excluding pharmacy cost component (=$1368 - $806)

[e] National Consolidated Cost Weights for AR DRG Version 5.2 - Round 13, 2008-09; Private Sector, Item R63Z, Chemotherapy excluding pharmacy cost component (=$459 - $128)

## Proposed structure of economic evaluation (decision analysis)

The decision analysis provided in Figure 3 is suitable for the trial population based analysis where the staging of the tested population is identical to the staging of the population who would be eligible for vemurafenib.

The decision analysis provided in Figure 4 allows for the tested population to also include patients who have not yet progressed to the staging of the population who would be eligible for vemurafenib. The structure of this decision analysis reflects the fact that some of these patients may not progress to become suitable for vemurafenib or chemotherapy. It is expected that the tested populations incorporated in this decision analysis would vary according to the other scenarios delineated in Table 4. Therefore, the incremental cost effectiveness would be explored for each of the other definitions of population staging described in Table 4 according to the clinical management outline provided in Figure 3.

These decision analyses allow provision for the use of linked evidence ie by breaking down the outcomes into true positives and false positives, and true negatives and false negatives. However, with direct trial evidence of the impact of BRAF genetic testing and targeted treatment on health outcomes and complete analytical concordance across all BRAF genetic test options available, these arms could be collapsed so that health outcomes from a positive test result are provided and health outcomes from a negative test result are provided, as the impact of false positives and false negatives will then be measured by the overall mix of health outcomes. The assessment of the comparative analytical performance and clinical validity of the different BRAF genetic test options is therefore essential to inform the applicability of the direct trial evidence and to inform an assessment of the other scenarios.

**Figure 3** Decision tree representing the decision options of publicly funding BRAF genetic testing to guide treatment in patients with melanoma where the staging of patients tested is identical to the staging of patients eligible for vemurafenib

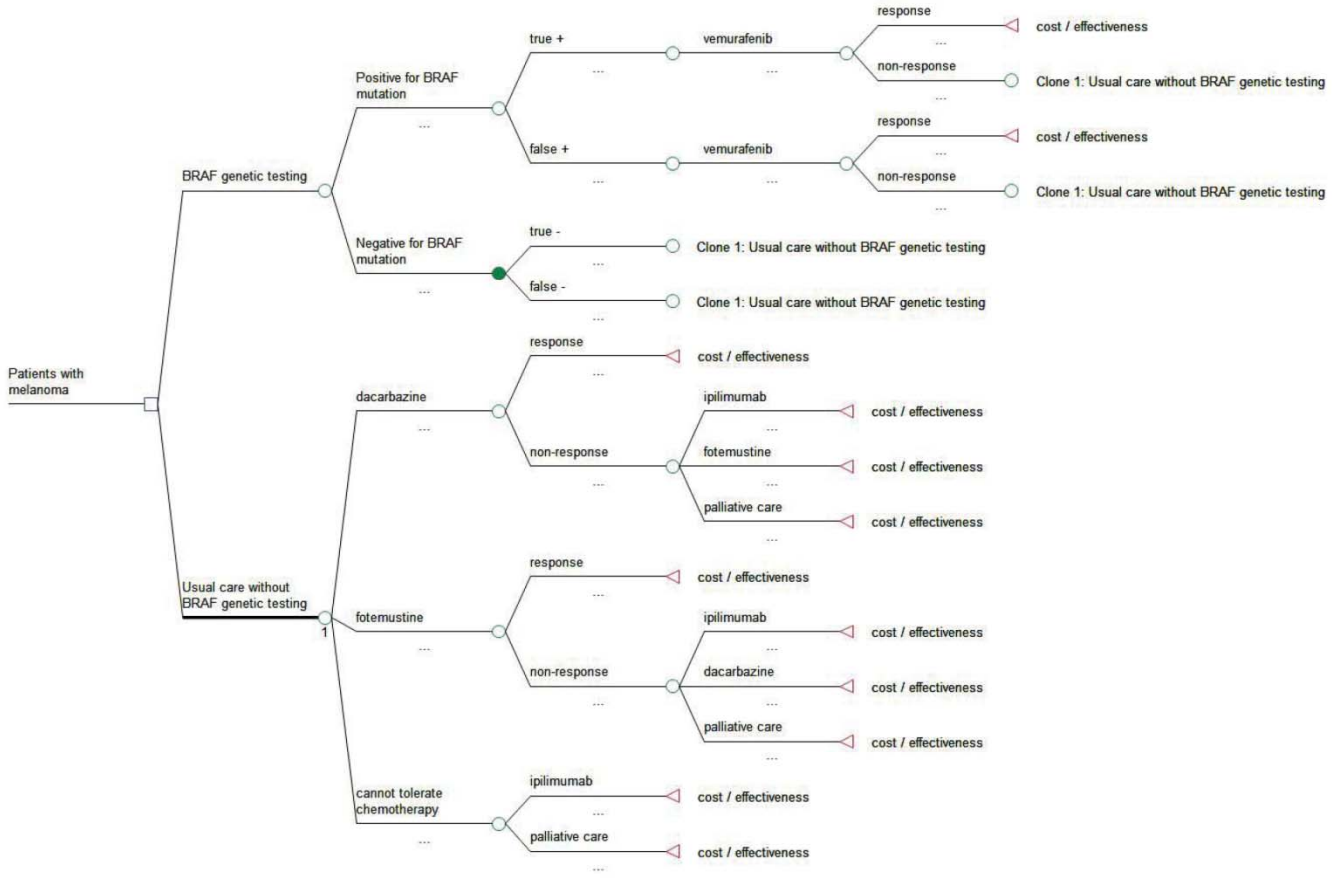
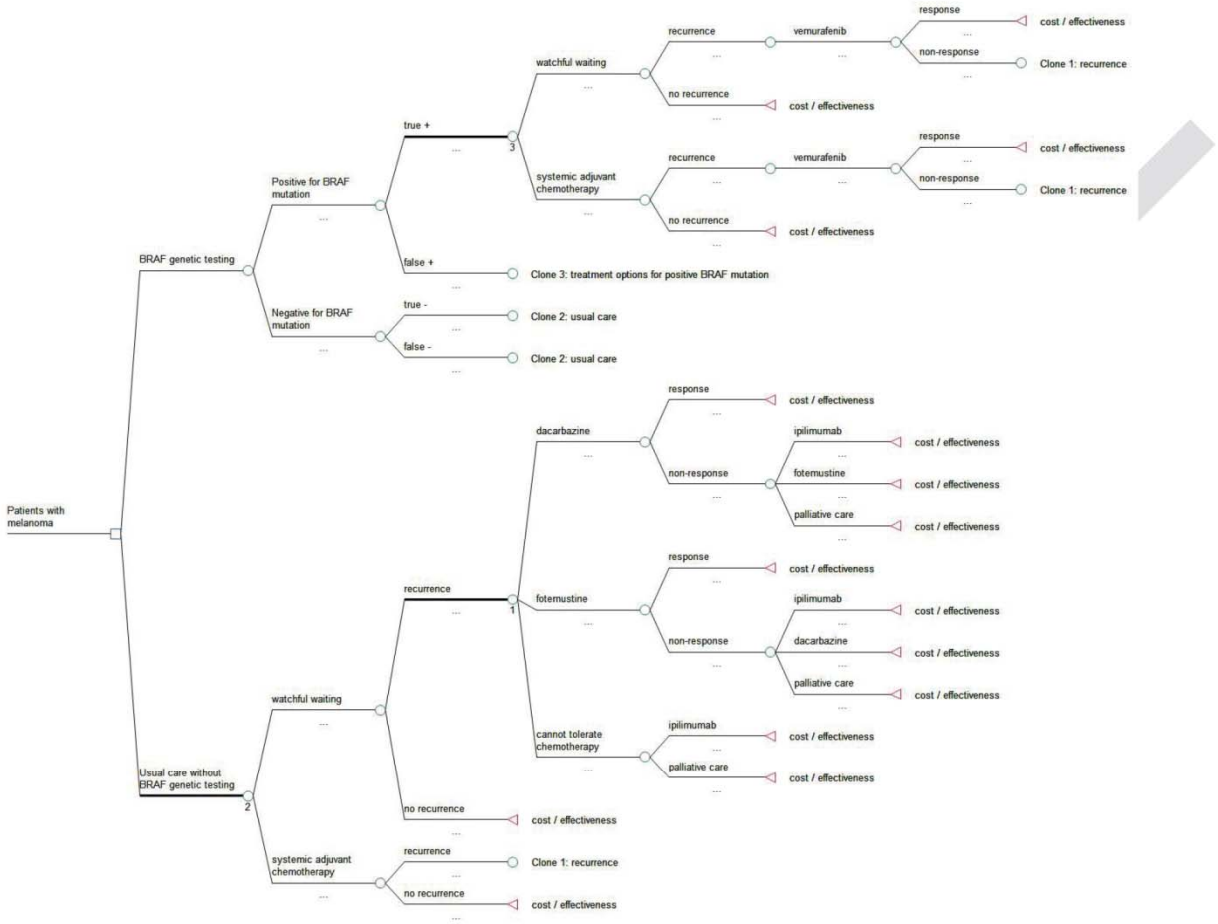


**Figure 4** Decision tree representing the decision options of publicly funding BRAF genetic testing to guide treatment in patients with melanoma where the staging of patients tested also includes stages earlier than the staging of patients eligible for vemurafenib



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