Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1153 – Genetic Testing for Hereditary Mutations in the VHL Gene that Cause von Hippel-Lindau (VHL) syndrome

Applicant: **Pathology Services Table Committee**
Date of MSAC consideration: **54th MSAC meeting, 29 November 2011**

1. Purpose of application

On November 2010, the Pathology Services Table Committee (PSTC) requested that the Medical Services Advisory Committee (MSAC) undertake an assessment of genetic testing for hereditary mutations in the VHL gene that cause VHL syndrome for (i) patients with symptoms of VHL syndrome, and (ii) family members of a patient with a confirmed diagnosis of VHL syndrome.

The proposed intervention is for VHL genetic testing that would be required to be performed once for each patient, with the following two different types of delivery occurring:

(i) Diagnostic VHL genetic testing of patients suspected of having VHL syndrome would be used in addition to the existing clinical diagnostic service during the non-acute stage of patient management, that is, after the initial presentation, diagnosis and treatment of the presenting complaint. In patients with unequivocal VHL syndrome, the genetic test adds no further information for their care, and continuing surveillance for other manifestations of the syndrome is indicated on clinical grounds. In patients with suspected VHL syndrome the genetic test identifies patients for whom continuing surveillance for other manifestations of the syndrome is indicated.

(ii) Pre-symptomatic or predictive VHL genetic testing would be performed as a non-urgent test once a VHL mutation has been identified in a family. Pre-symptomatic testing can be offered, after accredited genetic counselling, to first-degree family members (mother, father, offspring and sibling) and, as appropriate, second-degree family members (grandparent, half-sibling, aunt, uncle, niece, nephew and cousin).

VHL syndrome is an autosomal dominant neoplastic disease caused by germ-line mutations or deletions in one copy of the VHL tumour suppressor gene located on chromosome 3p25. Tumours arise when spontaneous mutations occur in the second copy of the VHL gene in individual cells of affected organs. It is suggested that patients presenting with one or more characteristic tumours or a positive family history of VHL syndrome should be screened to determine if there is a germ-line mutation in the VHL gene.

VHL syndrome is a progressive disease of diverse nature, with a high frequency of multiple neoplastic lesions in various organ systems. Individuals who have inherited the VHL mutation would be offered a lifelong screening program and early intervention to reduce the risk from, or severity of, VHL-associated neoplasms. A positive VHL genetic test will not affect the requirement for annual screening, and there would be no change in the use of co-administered screening interventions. For patients with suspected VHL syndrome, a positive VHL genetic test makes the diagnosis of VHL syndrome and indicates that screening interventions are warranted. However, if accurate, a negative VHL genetic test would eliminate the requirement for annual screening from

patients suspected of having VHL syndrome. Thus, the test will replace the routine clinical screening interventions for these patients.

VHL syndrome affects approximately 1 in 91,000 people worldwide. It is characterized by both benign and malignant tumours in specific organs of the body, including the central nervous system, eye, inner ear, kidney, pancreas, adrenal gland, and epididymis in the male and broad ligament in the female.

The mean age of onset of VHL disease is 26 years, and 90% of affected individuals will show signs of the disease by 65 years of age. The life expectancy is similar to the norm due to improved screening guidelines, with mortality mostly due to metastases of clear-cell renal cell carcinoma and complications of haemangioblastomas of the central nervous system.

The proposed medical services are not covered under any existing Medicare Benefits Schedule (MBS) item. Patients currently have their blood sample collected through a public hospital, in which case that facility may be charged for the genetic testing. Alternatively, when patients are referred by a private facility, they are billed directly.

2. Background

There has been no previous MSAC consideration of genetic testing for hereditary mutations in the VHL gene that cause VHL syndrome.

3. Prerequisites to implementation of any funding advice

In vitro diagnostic medical devices (IVDs) are, in general, 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 Therapeutic Goods Administration (TGA) regulatory framework for IVDs changed in July 2010, such that in-house laboratory tests now receive a similar level of regulatory scrutiny as commercial kits. As testing for VHL is currently only provided by laboratories, it would be classified as a Class 3 in-house IVD. Laboratories that manufacture in-house Class 3 IVDs are required to notify the TGA of the types of IVDs manufactured in their laboratory for inclusion on a register. These laboratories must have 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 (Therapeutic Goods Administration 2011).

4. Proposal for public funding

The applicant's proposed MBS items are listed below:

Category 6–Pathology services
MBS [item number] (proposed MBS item 1) Detection of germ-line mutations of the *VHL* gene in: (i) Patients with a clinical diagnosis of VHL syndrome: • a family history of VHL and a haemangioblastoma (retinal or CNS), phaeochromocytoma or renal cell carcinoma • two or more haemangioblastomas, or one haemangioblastoma and a visceral tumour (with the exception of epididymal and renal cysts, which are frequent in the general population) (ii) Patients presenting with one or more clinical features suggestive of VHL syndrome: • haemangioblastomas of the brain, spinal cord, and retina • phaeochromocytoma or functional extra-adrenal paraganglioma Fee: $600 Prior to ordering these tests, the ordering practitioner should ensure that the patient has given informed consent. Testing can only be performed after genetic counselling. Appropriate genetic counselling should be provided to the patient by a genetic counselling service or a clinical geneticist on referral. Further counselling may be necessary upon receipt of the test results.

MBS [item number] (proposed MBS item 2)

Detection of germ-line mutations of the *VHL* gene in: (i) Biological relatives of patients with a known mutation in the *VHL* gene Fee: $340 Prior to ordering these tests, the ordering practitioner should ensure that the patient has given informed consent. Testing can only be performed after genetic counselling. Appropriate genetic counselling should be provided to the patient by a genetic counselling service or a clinical geneticist on referral. Further counselling may be necessary upon receipt of the test results.

It is expected that the MBS item for the testing of relatives would primarily be used for first- and second-degree relatives, but the proposed listing has been kept broad to allow for exceptional circumstances where wider use may be required.

MSAC suggested that diagnostic testing for heritable mutation in affected patients and diagnostic testing for somatic mutations in patients with VHL syndrome and normal germline study be available to specialists involved in the management of patients with VHL syndrome but that predictive test for heritable mutation in relative of person with a heritable mutation be restricted to clinical geneticists.

MSAC noted that most current testing is done outside the Medicare system and 16% of laboratories performed less than 100 genotype tests in one year, with many laboratories who do very few diagnostic tests falling outside the scope of NATA volume threshold criteria. MSAC suggested that all testing should be ordered by a clinical geneticist or through a family cancer clinic or general genetics clinic – whose roles would include interpretation of unclassified variants and negative tests. MSAC also noted that MBS listing of this test would be contingent on an accredited quality assurance program to support the delivery of the test.

MSAC noted that laboratories offering the test in-house must have National Association of Testing Authorities 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, for each test manufactured.

5. Consumer Impact Statement

The public was invited to provide feedback on the draft protocol for undertaking this evaluation of VHL testing during March 2011. The responses were from specialists and a researcher. The perceived benefits and disadvantages arising from genetic testing for the presence of germ-line VHL mutations in symptomatic patients and their asymptomatic at-risk relatives are summarised below:

Benefits

Providing equity of access to VHL genetic testing across the country avoids local variations in funding arrangements for genetic testing provided by the states.

Patients will no longer be affected by limited annual genetic testing budgets. Medicare listing will permit more patients with suspected VHL syndrome to be identified, with the attendant benefits to themselves and their asymptomatic family members, through cascade testing.

Patients desire clarity in their diagnosis and the VHL genetic test would allow this.

For a patient or family member that tests positive, it will provide confirmation of a VHL syndrome clinical diagnosis. It may also facilitate patient compliance with the intense surveillance that is necessary with the condition.

For a patient or family member that tests negative, it would provide confidence that they do not have undiagnosed VHL syndrome. In patients with clinical symptoms, this exclusion of VHL would allow a differential diagnosis to be undertaken. A negative test result would also exclude the necessity for intense long-term surveillance for neoplasms, reduce the associated stress on the individual/family, and limit any possible impact on reproductive choices.

Disadvantages

Testing must be done in the setting of a clinical genetics unit, or in collaboration with a clinical genetics unit, for adequate management of expectations regarding sensitivity/specificity of testing and implications of results.

There may be family pressure to be tested; hence, genetic counselling is essential.

For a patient with a clinical diagnosis of VHL and a positive genetic test result, there would be little change to circumstances as it is simply a confirmation or genetic explanation for a condition already known to be present.

For asymptomatic family members with a positive genetic test result, certain knowledge of a known predisposition to VHL syndrome could be overwhelming, causing psychological harm—although, with pre-test counselling from a clinical genetics unit or similar service, there are seldom major long-term problems.

6. Proposed intervention's place in clinical management

The proposed intervention is to be used in addition to the existing service.

Individuals who have inherited the VHL mutation would be offered a lifelong screening program and early intervention to reduce the risk from, or severity of, VHL-associated neoplasms. For patients with confirmed VHL syndrome, a positive VHL genetic test will not affect the requirement for annual screening, and there would be no change in the use of co-administered screening interventions.

However, for individuals with suspected VHL syndrome, a negative VHL genetic test would eliminate the requirement for annual screening. Thus, the test will replace the routine clinical screening interventions for these patients.

A management algorithm for both the diagnostic and predictive uses of VHL genetic testing was presented in the report (page 7). The left side of the algorithm explains the approach to the diagnosis and prediction of VHL syndrome in a setting without genetic testing (which is assumed to be the current approach, although it is acknowledged that some patients currently receive genetic testing without it being funded by the MBS). The right side of the algorithm shows the proposed approach in which genetic testing is available.

The main difference between the algorithm is the targeted use of lifelong surveillance in patients who have suspected but clinically unconfirmed VHL syndrome (and who have a VHL mutation), with fewer patients overlooked for surveillance due to a failure to diagnose the syndrome on clinical grounds alone (clinical false negative), and the lack of requirement for surveillance for family members who have not inherited the VHL mutation

7. Other options for MSAC consideration

<u>Somatic VHL genetic testing of CNS haemangioblastomas</u>

Currently, patients presenting with isolated CNS haemangioblastomas are routinely tested for both germ-line VHL mutations and somatic VHL mutations in the tumour itself.

However, the proposed MBS items do not allow for reimbursement for somatic VHL genetic testing as the descriptor has been limited to the 'detection of germ-line mutations of the VHL gene'.

<u>Prenatal and pre-implantation VHL genetic testing</u>

With increased understanding of the consequences and likelihood of having children affected by a familial VHL mutation, parents are looking for ways to ensure that their offspring are unaffected. They have two main options.

- Prenatal diagnostic tests such as chorionic villus sampling and amniocentesis, which are only useful if the parents were willing to abort the affected foetus. Amniocentesis also has an

associated risk of miscarriage. Prenatal predictive VHL genetic testing would not be reimbursed under Medicare as the foetus is not considered an 'eligible person' for health insurance.

- Pre-implantation genetic diagnosis, which is performed on the embryo prior to implantation and is only offered in the private setting in Australia. The Victorian Assisted Reproductive Treatment Authority lists the VHL gene as one of the single gene disorders that were tested using pre-implantation genetic diagnosis in 2010.

8. Comparator to the proposed intervention

Diagnosis of VHL syndrome is currently based on clinical criteria. Patients with a family history and a haemangioblastoma (including retinal), phaeochromocytoma or renal cell carcinoma are diagnosed with the disease. Those with no relevant family history must have two or more haemangioblastomas, or one haemangioblastoma and a visceral tumour (with the exception of epididymal and renal cysts, which are frequent in the general population), to meet the diagnostic criteria.

The healthcare resources required to clinically diagnose and monitor patients with VHL syndrome and asymptomatic family members with a confirmed VHL mutation would be the same for both intervention and comparator. Only family members with no pathogenic mutations in the VHL gene do not require clinical screening.

9. Comparative safety

No studies were identified that could inform an assessment of the safety of genetic testing in the diagnosis of VHL syndrome or for the identification of family members with a VHL mutation.

MSAC noted ESC advice that there were no studies identified that could assess the safety of genetic testing in the diagnosis of VHL syndrome or for the identification of family members with a VHL mutation. However, even with a lack of evidence relating to safety, the likelihood of adverse events as a consequence of VHL genetic testing is low. It was recognised that there are some risks associated with genetic testing that relate to minor injuries associated with venepuncture, as well as psychological harms (such as anxiety whilst awaiting for results), and possibly physical harms due to delayed or inappropriate treatment.

10. Comparative effectiveness

Direct Evidence

No comparative direct evidence was identified that reported a change in patient health outcomes following genetic testing either i) in addition to usual clinical diagnosis when compared with usual clinical diagnosis alone in patients suspected of having VHL syndrome or ii) when used as a triage test for lifelong screening of their family members.

Ten case series reported on the likelihood of VHL mutation positive patients developing various VHL-associated neoplasms. Three studies examined the likelihood of patients with a VHL mutation suffering from vision loss or blindness due to the presence of, or treatment for, retinal haemangioblastomas. Two studies reported on health outcomes in VHL mutation positive patients with renal cell carcinoma.

Linked Evidence - diagnostic accuracy of VHL genetic testing in patients suspected of having VHL syndrome

Eighty-one studies met the inclusion criteria outlined a priori and reported on the analysis of VHL mutations in the diagnosis of VHL syndrome in patients presenting with one or more VHL-associated neoplasms. Fifty-six comparative studies provided data on the diagnostic accuracy (level III-2 diagnostic evidence) of genetic testing alone, compared with current clinical diagnosis alone for patients who could potentially have VHL syndrome. Twenty-four studies only included patients who had all been clinically diagnosed with VHL syndrome.

Twenty-three case series reported on the diagnostic yield (level IV diagnostic evidence) of genetic testing for VHL mutations when used to diagnose patients presenting with clinical signs of disease. Sixteen studies, divided into three groups, provided diagnostic yield data for VHL genetic testing of patients diagnosed with phaeochromocytomas.

Four studies provided diagnostic yield data for VHL genetic testing of patients with familial phaeochromocytomas but no other symptoms for syndromic diseases such as VHL or MEN 2.

Linked Evidence - diagnostic accuracy of VHL genetic testing in family members of patients with a known VHL mutation

Forty-one studies met the inclusion criteria outlined a priori and reported on the analysis of VHL mutations in the pre-symptomatic genetic testing of close relatives of index patients (or probands) that carry a known VHL gene mutation. Fifteen studies provided comparative data (level III-2 diagnostic evidence) reporting on the predictive accuracy of genetic testing compared with clinical diagnosis in first-degree relatives (4 studies) or a combination of first- and second-degree relatives (12 studies). Twenty-six studies reported on the diagnostic yield (level IV diagnostic evidence) of pre-symptomatic genetic testing of first-degree relatives (12 studies), second-degree relatives (2 studies), and a combination of first- and second-degree relatives (17 studies).

Direct Evidence

The data obtained highlighted the health benefits resulting from annual screening but provided no information on the direct effectiveness of genetic testing in addition to current clinical management. Any health benefits would stem from early detection and treatment of newly developed VHL-associated neoplasms and thus reduced morbidity and mortality. As the annual screening protocol is identical for all VHL syndrome patients, irrespective of their VHL mutation status, and their at-risk family members, the lack of comparative data was predictable.

Linked Evidence - diagnostic accuracy of VHL genetic testing in patients suspected of having VHL syndrome

The current standard VHL genetic testing methods of direct DNA sequencing of PCR products from all three exons of the VHL gene, plus a method to detect large deletions of the VHL gene such as MLPA, should be highly accurate. The median sensitivity, specificity, and positive predictive and negative predictive values, for these genetic tests were uniformly high. However, the false negative rate of 10.2% suggests that detection of a germ-line mutation is not yet possible for some patients with VHL syndrome. Thus, VHL genetic testing should not be used as a standalone test for the diagnosis of VHL syndrome. Clinical diagnosis of VHL syndrome is still required for patients presenting with VHL-related neoplasms.

The false positive rate of 4.2% was expected, as there will always be a few patients who do not currently meet the criteria for clinical diagnosis of VHL syndrome but have an underlying VHL mutation. In these patients the disease would be expected to progress such that a positive clinical diagnosis would be made in the future.

Patients with familial phaeochromocytomas have a 50% probability of having a VHL mutation that is indicative of type 2C VHL syndrome.

Linked Evidence - diagnostic accuracy of VHL genetic testing in family members of patients with a known VHL mutation

Once an index case has a pathogenic VHL mutation identified, their close relatives need only be tested for that specific mutation, using a testing methodology known to be able to detect that type of mutation. Thus, every included study reporting accuracy data for relatives of a patient with a known VHL mutation reported a sensitivity of 100%. The median specificity of 83.3–85.0% and the false positive rates of 16.9–23.5% reflect the difference in the timeframe required for a positive clinical diagnosis compared with a positive genetic test. Younger relatives are more likely to receive a positive genetic test before any clinical signs of disease can be detected by clinical screening.

Approximately 4 out of 10 of all first- and second-degree relatives, and 2–3 out of 10 asymptomatic first- and second-degree relatives that undergo VHL genetic testing were identified as carriers of the familial VHL mutation.

Some evidence was identified regarding patient management following diagnosis of VHL syndrome using genetic testing in combination with clinical diagnosis, but none provided a direct comparison between patients who had been genetically tested and those who had not been tested. Due to the lack of an appropriate comparator group, no conclusions can be made about the change in patient management (ie the clinical impact) from genetic testing.

Interestingly, only 38.9% of patients with a VHL mutation continued screening after 5 years. Symptomatic patients were more likely to continue than asymptomatic patients. Patients who have symptoms or have a neoplasm detected early are more aware of the personal risks involved than patients who have not developed any detectable neoplasms.

While 88.0–97.0% of clinically diagnosed VHL patients agreed to genetic testing, only 58.5–65.8% of at-risk relatives agreed. Additionally, relatives aged over 20 years were more likely to undergo genetic testing than children aged less than 5 years, suggesting that parents are reluctant to have very young children genetically tested.

MSAC members noted that it is plausible that earlier monitoring may lead to earlier treatment and improved health outcomes. There were 81 studies that met the inclusion criteria outlined a priori that reported on the analysis of VHL mutations in the diagnosis of VHL syndrome in patients presenting with one ore more VHL associated neoplasms. There were 41 studies that met the inclusion criteria outlined a priori that reported on the analysis of VHL mutations in family members of patients with a known mutation.

11. Economic evaluation

A cost comparison was performed due to the absence of direct evidence for the increased effectiveness of the addition of genetic testing to clinical testing. The assumption of equal effectiveness is a conservative one.

The analysis considered the costs associated with an individual suspected of having VHL syndrome (the index case) and the costs associated with testing and monitoring (annual screening) their first and second degree relatives (who are at risk of having the VHL mutation). The first part of the analysis delivered individuals or family members into either monitoring or no-monitoring health states based upon the best information known from either genetic and clinical testing or clinical testing alone. A proportion of family members are assumed to refuse genetic testing (40%) and a proportion to refuse monitoring (60%). This non-compliance is a more realistic situation than 100% adoption of either testing or monitoring, and is important to consider because it will tend to dilute the cost savings associated with the genetic testing arm. Those who are genetically positive (whether this status is known or unknown) but refuse monitoring will transit to a monitoring state once they become symptomatic.

Due to the high sensitivity and specificity of the genetic test compared with a clinical diagnosis, there was very little difference in costs associated with managing the index case between the two arms, except for the cost of the VHL diagnostic test and the genetic counselling. However, when applied to family members, who have an assumed likelihood of carrying the VHL mutation of 26%, there is a marked decrease in monitoring among those who do not require monitoring (22.1%).

Costs of monitoring were assumed to be accrued over a lifetime, with mortality estimated from the Australian life tables (Australian Bureau of Statistics 2010a). Treatment costs are assumed to be equivalent in both arms.

The overall cost saving (through avoided inappropriate monitoring) of a single index case and their family over their lifetimes is $7,749 in discounted costs and $20,783 in undiscounted costs. As there are many uncertainties in the analysis, several sensitivity analyses have been performed. The cost comparison is most sensitive to the prevalence of VHL syndrome among patients who are

suspected of having it, and the uptake of genetic testing and monitoring among family members. In most sensitivity analyses, a cost saving remains following the introduction of VHL genetic testing. Furthermore, if monitoring and genetic testing rates among family members increase, the cost saving associated with genetic testing will markedly increase. The cost comparison is not sensitive to moderate changes in the proposed MBS reimbursement for VHL genetic testing.

MSAC members noted that a long-term Markov model was constructed and the model time horizon was set at 100 years as some family members would be diagnosed or monitored from a very young age.

It is likely that the costs associated with managing individuals suspected of having VHL syndrome and their families are fewer when genetic and clinical testing is available, compared with clinical testing alone. This is largely driven by the reduction of monitoring in family members who are not at risk of developing VHL syndrome.

The applicant proposed a fee of $600 for the diagnostic test to detect germ-line mutations in the VHL gene, and a fee of $340 for a predictive test to detect mutations in the VHL gene in family members of a proband.

The cost of monitoring will be different depending upon the age of the patient who is being monitored and, for simplicity, all patients are assumed to be adults. It is important to note that the cost of monitoring would be incurred in the absence of genetic testing and is not a consequence of the introduction of the VHL test. The costs associated with the introduction of genetic testing are difficult to represent.

MSAC members were unsure of the costs associated with genetic counselling and the lifelong screening program (cost of monitoring will be different depending upon the age of patient).

As the test result is definitive, VHL genetic testing would only need to be performed once for each patient.

12. Financial/budgetary impacts

As the test result is definitive, VHL genetic testing would only need to be performed once for each patient.

Current usage of the VHL diagnostic test is estimated at 80 tests per year. This is based on data from 2006 to 2007 and may be a high estimate if this was a period of testing a 'backlog' of patients. It has been assumed that the number of tests will increase to 160 per year over five years following the listing of VHL genetic testing on the MBS. Again, this may be high and therefore represents a conservative estimate.

Usage of the VHL predictive test is assumed to be 30 per year and will not increase because the numbers rely upon the identification of a VHL mutation rather than any increase in the use of the VHL genetic test.

Expected number of diagnostic and predictive tests for patients suspected of having VHL syndrome and their family members

	Costs associated with the introduction of genetic testing for suspected VHL syndrome				
	2012	2013	2014	2015	2016
Diagnostic testing (n)	80	100	120	140	160
Predictive testing (n)	30	30	30	30	30

It VHL genetic testing is listed on the MBS, the total cost for testing and counselling to the Australian healthcare system will be between $86,100 (based on 80 diagnostic tests) and $154,400 (based on a doubling of diagnostic tests) per year. The costs borne by the MBS for these scenarios will be $64,600 and $115,800 respectively.

Annual cost of testing and counselling for patients suspected of having VHL syndrome and their family members

	Costs associated with the introduction of genetic testing for suspected VHL syndrome				
	2012	2013	2014	2015	2016
Diagnostic genetic testing	$48,000	$60,000	$72,000	$84,000	$96,000
Predictive genetic testing	$10,200	$10,200	$10,200	$10,200	$10,200
Genetic counselling	$27,929	$33,007	$38,085	$43,163	$48,241
Total	$86,129	$103,207	$120,285	$137,363	$154,441

The setting in which the genetic testing and monitoring is undertaken will determine who is responsible for the cost. If the genetic test is listed on the MBS, there may be an increase in referrals from the private health system. It has been assumed that 25% of services will be performed in the private healthcare system, and in these cases the patient, or private insurance, will reimburse the proportion of the costs not covered by the MBS. In the public health system it is assumed that the state/territory governments, rather than patients, will cover the costs not borne by the MBS. For genetic counselling, 75% of the fee is assumed to be reimbursed by the MBS in both the private and public sectors, with the patient and the state/territory government covering the 25% gap. However, while it is likely that the specialist (clinical geneticist) will provide genetic counselling in private, it is unclear how prevalent this may be in the public sector, where genetic counsellors (who are not medical specialists) are employed. It is likely that a proportion of patients will be provided genetic counselling in the public sector and the state/territory government will absorb the costs, at a saving to the MBS. Due to the inability of genetic counsellors to receive payment from the MBS (and are therefore funded by the state/territory governments), there may be an incentive to use specialists for genetic counselling over genetic counsellors, despite the higher cost associated with the service.

Unit costs for genetic tests, counselling and annual monitoring separated by MBS, other government or patient

Based on 75% of services delivered in the public sector	Cost	MBS	Other government	Patient/ insurer
Genetic testing of an individual	$600.00	$450.00	$112.50	$37.50
Genetic testing of family members	$340.00	$255.00	$63.75	$21.25
Genetic counselling	$253.90	$190.43	$47.61	$15.87
Annual monitoring costs of adults with suspected VHL syndrome	$686.85	$515.14	$128.78	$42.93

The costs avoided through improvements in targeted monitoring will increase annually as an increasing number of people are spared lifelong monitoring. In five years, based on sparing monitoring for ten people per year, the saving to the Australian healthcare system will be $34,300, of which $25,800 will be saved by the MBS.

Annual costs to the MBS, other governments and patients of genetic testing and genetic counselling, with cost savings from avoided monitoring

Total costs (50% reduction in monitoring)	2012	2013	2014	2015	2016
MBS	$59,445	$67,103	$74,760	$82,417	$90,074
Other government	$14,861	$16,776	$18,690	$20,604	$22,518
Patient/insurer	$4,954	$5,592	$6,230	$6,868	$7,506
Total	$79,261	$89,470	$99,680	$109,889	$120,099

Overall, the cost of genetic testing to the Australian healthcare system, accounting for savings associated with avoided monitoring, will be between $79,300 and $120,000.

MSAC noted the cost of lifelong screening would be incurred regardless of whether the test is included on the MBS in those individuals who had inherited the mutation or for those patients who are diagnosed with the VHL syndrome.

13. MSAC Key Issues

- Main issues around the evidence and conclusions for safety?

MSAC noted there were no studies identified that could inform an assessment of the safety of genetic testing in the diagnosis of VHL syndrome or for the identification of family members with a VHL mutation.

- Main issues around the evidence and conclusions for clinical effectiveness?

MSAC noted:

- that there was no direct evidence for increased effectiveness of the addition of genetic testing to clinical testing, however; earlier monitoring may lead to earlier treatment and improved health outcomes;
- patients whose genetic test shows that they do not have the mutation may be spared uncomfortable or unsafe monitoring investigations;
- family members may avoid the impact upon quality of life associated with lifelong screening or the psychological impact of not knowing one's genetic status;
- family members who would normally not be screened (because they are third-degree or more distant from the clinically diagnosed VHL patient) may be appropriately monitored and receive improved health outcomes; and
- only three pathology laboratories currently offer VHL genetic testing in Australia, using assays developed in-house.

- Main economic issues and areas of uncertainty?

MSAC was confident that savings in the long term would materialise by testing family members, with the real benefit to those family members who test negative which would result in a reduction of monitoring in family members who are not at risk of developing VHL syndrome.

MSAC noted that the current usage of the VHL diagnostic test is estimated at 80 tests per year and it has been assumed that the number of tests will increase to 160 per year over five years if VHL genetic testing is listed on the MBS. Usage of VHL predictive tests are assumed to be 30 per year and will not increase because the numbers rely upon the identification of a VHL mutation rather than any increase in the use of the VHL genetic test.

14. Other significant factors

MSAC noted advice from the Applicant comments on the ESC Report that there is currently a review of genetics services underway that is tasked with developing a national genetics framework.

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

On November 2010, the Pathology Services Table Committee (PSTC) requested that the Medical Services Advisory Committee (MSAC) undertake an assessment of genetic testing for hereditary mutations in the VHL gene that cause von Hippel-Lindau (VHL) syndrome for (i) patients with symptoms of VHL syndrome, and (ii) family members of a patient with a confirmed diagnosis of VHL syndrome.

VHL syndrome is a relatively rare clinical diagnosis of what is largely an inherited disorder that affects approximately 1 in 91,000 people worldwide. It is characterised by both benign and malignant tumours in specific organs of the body, including the central nervous system, eye, inner ear, kidney, pancreas, adrenal gland, and epididymis in the male and broad ligament in the female.

VHL syndrome generally occurs in individuals with a heritable (germline) mutation on one VHL gene. MSAC noted that there is strong evidence that von Hippel-Lindau syndrome is caused by germline sequence changes (70-80%) or large deletions (20-30%) in the VHL gene, and that the analytic validity of a test which incorporates direct DNA sequencing and a deletion screen will provide an accurate assessment of genetic changes in this gene.

Cells in an individual with a germline mutation in one VHL gene maintain normal function until a second normal copy (allele) of the VHL gene in a cell succumbs to random (somatic) mutation, allowing the development of a tumour. Heritable mutation therefore places the patient and relatives at risk of other tumours. Somatic mutations (occurring after conception but still whilst in utero) of both alleles of the VHL gene in a cell can also cause tumours, but these mutations are not-heritable. A person with a germline VHL mutation has a greater than 90% lifetime risk of developing a tumour(s). MSAC noted that genetic testing for VHL mutations potentially provides an opportunity for screening for tumours in affected individuals and the possibility of identifying the relatives of patients who have been diagnosed with a heritable mutation who are 'at risk of the syndrome' before they develop clinical features of the syndrome.

90% of affected individuals will show signs of the disease by 65 years of age, and the mean age of onset of VHL syndrome (identification of tumours) is 26 years. Improved screening of affected individuals has resulted in their life expectancy being similar to the norm, with premature mortality mostly due to metastases of clear-cell renal cell carcinoma and complications of haemangioblastomas of the central nervous system.

The comparator used for assessing the performance of VHL testing was patients with diagnosed VHL syndrome.

There were no studies identified that could assess the safety of genetic testing in the diagnosis of VHL syndrome or for the identification of family members with a VHL mutation. However the likelihood of adverse events as a consequence of VHL testing are low.

Assessments of the analytic validity of VHL testing using DNA sequencing and deletion studies have shown a median sensitivity and specificity of greater than 90%. False negative results (10%) may occur where two tumours independently arise from only somatic mutations (in the absence of a germline mutation) that are localised to the tumour tissue and are therefore not detected when other tissues such as peripheral blood are tested.

An overall assessment of the evidence in relation to clinical validity suggests that the detection of a VHL mutation corresponds acceptably well with patient clinical consequences. Ten case series described the prevalence of *VHL* tumours in mutation positive patients and their mean age of onset, which confirmed the clinical description of the syndrome, but added little in terms of assessing the clinical validity of *VHL* testing. Accordingly, 100% of relatives of the index case who also have VHL syndrome can be expected to have the mutation detected (sensitivity). On the other hand, studies show that 50-100% of people with the mutation can be expected to have VHL syndrome (specificity) at the time of testing. MSAC agreed that there was a biologically plausible explanation for this specificity range in that it can be expected that a proportion of relatives who are found to

have the VHL mutation but who do not express clinical features of VHL syndrome at the time of testing are likely to do so over time. This correlates with variable reports on the predictive positive value of the test (ie some carriers do not have symptoms at the time of testing). The negative predictive value of the test is 100% (ie all relatives who do not have the mutation do not develop VHL syndrome).

MSAC noted that there was no direct evidence that *VHL* germline mutation testing changed health outcomes for patients already diagnosed with VHL syndrome, because patients who had a clinical diagnosis of von Hippel-Lindau syndrome would be enrolled in surveillance irrespective of the results of germline testing. The clinical utility of testing was most likely to be manifested in a) unaffected relatives of patients with a positive *VHL* test; and b) tumour-affected individuals in whom the diagnosis of von Hippel-Lindau disease was uncertain. The identification of a *VHL* mutation in these individuals would prompt a recommendation for life-long surveillance while unaffected relatives with a negative VHL test result could be reassured that screening was unnecessary. MSAC noted however that in reported studies, only 58-65% of unaffected relatives agree to predictive testing and that only 38.9% of patients with a *VHL* mutation continued screening after 5 years. Although there was no direct evidence to support the benefits of surveillance, one study showed that visual outcomes were improved if retinal haemangioblastomas were detected at an asymptomatic stage. It was also noted that prior to the introduction of screening for VHL patients, the median survival was less than 50 years and today the life expectancy is similar to the normal population. This change in life expectancy may be the consequence of early detection and treatment of VHL tumours.

The data indicated that the type of genotypic mutation in the *VHL* gene influences the clinical manifestations of the disease, that the clinical manifestations of *VHL* overlap with other genetic syndromes, and that 20% of VHL germline mutations arise *de-novo*. For these reasons, the probability of identifying a germline mutation in VHL was dependent on recognising a constellation of benign and malignant tumours (eg haemangioblastomas, renal cysts, renal cell cancer and pheochromocytoma) in both the affected individual and members of their family. On this basis, MSAC considered that diagnostic (in affected individuals) and predictive (in biological relatives of patients with a known mutation) germline testing should be ordered by medical specialists with expertise in the management of VHL in collaboration with a clinical genetics service for the management of this type of testing. MSAC agreed that for ethical reasons, predictive testing should only occur after genetic counselling.

In addition to germline mutation testing for diagnostic and predictive purposes, MSAC agreed that it was important to have an item descriptor to allow for testing of somatic mutations of the VHL gene in the tumour tissue of those with certain clinical characteristics suggestive of VHL syndrome but no germline mutation of the VHL gene identified by genetic testing. It was agreed that indications for somatic VHL mutation testing would be where germline VHL mutation negative patients had two or more tumours suggestive of VHL syndrome, being - two or more haemangioblastomas, or one haemangioblastoma and a tumour of the adrenal gland, kidney or pancreas.

Costs avoided through improvements in targeted monitoring will increase annually as an increasing number of people are spared lifelong monitoring on the basis of a negative test for a germline mutation of the VHL gene. MSAC considered these figures robust in the various sensitivity analyses - on the very conservative assumption that no health benefits are accrued to an individual from testing, the testing itself is still likely to result in a cost saving per family in the long term as a consequence of reduction in unnecessary monitoring of family members.

It is estimated that if the MBS listed the test for this indication, the number of diagnostic VHL mutation tests will increase from 80 per annum in 2012 to 160 in 2016; and the number of predictive VHL mutation tests will be in the order of 30 per annum (2012-2016).

MSAC noted that there were no definitive cost-effectiveness studies for this test. However economic modelling suggested that genetic testing would result in an increased overall net cost per

patient with VHL syndrome, but a decreased overall net cost per family. A cost comparison analysis showed that if 60% of family members accept genetic testing and 40% accept monitoring, the overall lifetime cost saving (through avoided inappropriate monitoring) of a single index case *and* their family (first and second degree relatives), the discounted cost of introduction of the test will be $7,749 ($20,783 undiscounted).

The net costs to MBS and to the health care system were small. Assuming 50% uptake of testing, net costs to the MBS would be $65,000 in 2012, increasing to $116,000 in 2016; and assuming 50% uptake of testing a net cost to the healthcare system would be $79,000 in 2012 increasing to $120,000 in 2016.

MSAC noted that most current testing is done outside the Medicare system and 16% of laboratories performed less than 100 genotype tests in one year, with many laboratories who do very few diagnostic tests falling outside the scope of NATA volume threshold criteria. MSAC suggested that all testing should be ordered by a medical specialist with expertise in the management of VHL or through a family cancer clinic or general genetics clinic – whose roles would include interpretation of unclassified variants and negative tests. MSAC also noted that MBS listing of this test would be contingent on an accredited quality assurance program to support the delivery of the test.

MSAC noted that MBS listing of the test is likely ensure equitable access to testing irrespective of the state or territory in which the patient resided.

On the totality of the evidence, MSAC concluded that diagnostic germline testing for *VHL* mutations in selected affected individuals and predictive germline testing for VHL in unaffected relatives; and somatic testing for VHL mutations in selected patients with features of VHL syndrome but no germline mutation of the VHL gene is likely to improve the mortality and morbidity of von Hippel-Lindau disease.

16. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to the safety, effectiveness and cost-effectiveness of genetic testing to evaluate von Hippel-Lindau disease, MSAC supported public funding for listing three tests on the MBS, as follows:

- Diagnostic test for heritable mutation in affected patient
- Predictive test for heritable mutation in relative of person with a heritable mutation
- Diagnostic test for somatic mutations in patient with VHL syndrome and normal germline study.

Draft item descriptors:

Diagnostic test descriptor

Detection of germline mutations of the *VHL* gene in

(i) patients with a clinical diagnosis of VHL syndrome:

- a family history of VHL **syndrome** and a haemangioblastoma (retinal or CNS), phaeochromocytoma or renal cell carcinoma **OR**
- two or more haemangioblastomas, or one haemangioblastoma and a tumour or cyst of the adrenal gland, kidney, pancreas, epididymis, and broad ligament (with the exception of epididymal and single renal cysts, which are frequent in the general population)

(ii) patients presenting with one or more clinical features suggestive of VHL syndrome:

- haemangioblastomas of the brain, spinal cord, **OR** retina**; or** phaeochromocytoma or functional extra-adrenal paraganglioma.

Predictive test descriptor

Detection of germline mutations of the *VHL* gene in:

(i) Biological relatives of patients with a known mutation in the *VHL* gene

Somatic test descriptor

Detection of somatic mutations of the *VHL* gene in two or more tumours from patients with
(i) two or more haemangioblastomas, or one haemangioblastoma and a tumour of the adrenal gland, kidney, pancreas, or epididymis, and
(ii) no germline mutation of the *VHL* gene identified by genetic testing.

17. Context for decision

This advice was made in accordance with MSAC Terms of Reference.

MSAC is to:

Advise the Minister for Health and Ageing on medical services that involve new or emerging technologies and procedures and, where relevant, amendment to existing MBS items, in relation to:

- the strength of evidence in relation to the comparative safety, effectiveness, cost-effectiveness and total cost of the medical service;
- whether public funding should be supported for the medical service and, if so, the circumstances under which public funding should be supported;
- the proposed Medicare Benefits Schedule (MBS) item descriptor and fee for the service where funding through the MBS is supported;
- the circumstances, where there is uncertainty in relation to the clinical or cost-effectiveness of a service, under which interim public funding of a service should be supported for a specified period, during which defined data collections under agreed clinical protocols would be collected to inform a re-assessment of the service by MSAC at the conclusion of that period;
- other matters related to the public funding of health services referred by the Minister.

Advise the Australian Health Ministers' Advisory Council (AHMAC) on health technology assessments referred under AHMAC arrangements.

MSAC may also establish sub-committees to assist MSAC to effectively undertake its role. MSAC may delegate some of its functions to its Executive sub-committee.

18. Linkages to other documents

MSAC's processes are detailed on the MSAC Website at: www.msac.gov.au. The MSAC Decision Analytic Protocol and Assessment Report are available at http://www.msac.gov.au/internet/msac/publishing.nsf/Content/app1153-1