# Protocol to guide the assessment of genetic testing for hereditary mutations in the VHL gene that cause von Hippel-Lindau syndrome

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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 analytic protocol that will be used to guide the assessment of genetic testing for hereditary mutations in the *VHL* gene for (i) patients with symptoms of von Hippel-Lindau (VHL) syndrome, and (ii) a family member of a patient with a confirmed diagnosis of VHL syndrome. The protocol has been finalised after inviting relevant stakeholders to provide input, including Members of the Expert Standing Panel (MESP).  It provides the basis for the evidence-based assessment of the intervention.

The protocol has been developed using the widely accepted "PICO" approach. This approach involves a clear articulation of the following aspects of the research questions that the assessment intends to answer:

> **P**atients – specification of the characteristics of the population or patients in whom the intervention is intended to be used;
> **I**ntervention – specification of the proposed intervention;
> **C**omparator – specification of the therapy most likely to be replaced, or added to, by 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 the application

In November 2010, an application from the Pathology Services Table Committee (PSTC) was received by the Department of Health and Ageing, requesting a MBS listing for 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.

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 has developed this decision analytic protocol and will undertake an independent assessment of the safety, effectiveness and cost-effectiveness of VHL testing in order to inform MSAC's decision-making regarding public funding of the intervention.

## Intervention

### Clinical need and burden of disease

VHL syndrome affects approximately 1 in 36,000 people worldwide and is characterised by both benign and malignant tumours in specific organs of the body including: the central nervous system, the eye, the inner ear, the kidney, the pancreas, the adrenal gland, and the 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 age 65 years. Before routine comprehensive screening, median survival of patients with VHL syndrome was less than 50 years (Lonser et al 2003). Today, the life expectancy is similar to the norm due to improved screening guidelines (Nordstrum-O'Brien et al 2010). Mortality is mostly due to metastases of clear-cell renal cell carcinoma and complications of haemangioblastomas of the central nervous system (Barontini and Dahia 2010; Nordstrum-O'Brien et al 2010).

**Haemangioblastomas** are the most common lesion associated with VHL syndrome. They are highly vascular benign tumours, but they may cause important neurological deficits. In early studies, 53% of patients with VHL syndrome died due to complications of cerebellar haemangioblastomas. As surgical techniques have improved, the death rate has fallen dramatically. Haemangioblastomas can occur sporadically, but in about 20–30% of cases they are a component tumour of VHL syndrome. Cerebellum and spinal cord tumours are the major central nervous system manifestations and affect 60–84% of patients with Type 1 or Type 2A and 2B VHL disease. Tumours develop from childhood (less than 10 years of age), but are more common in the third decade of life (Barontini and Dahia 2010).

**Retinal haemangioblastomas** are the typical ocular lesions of VHL syndrome. They are not malignant, commonly occur in individuals affected by VHL and are often the first sign of

disease. Retinal angiomas can lead to retinal detachment, blindness, cataracts, and (secondary) glaucoma (Koch, Walther & Linehan 2008). They are a sporadic tumour, usually occurring in older patients. They predominantly appear in the third decade of life, but any age from early childhood (less than 10 years of age) can be affected (Barontini and Dahia 2010).

**Renal cell carcinoma.** Patients with VHL syndrome are at high risk of developing multiple renal cysts and renal cell carcinoma (RCC), which occurs in about two-thirds of patients. They develop with increasing frequency from over 20 years of age and it has been reported that at the age of 60 years about 70% of patients with Type 1 and Type 2B VHL syndrome develop RCC (Barontini and Dahia 2010). Recent studies have suggested that a high proportion (86 to 95%) of sporadic conventional RCC have genetic or epigenetic changes to the *VHL* gene that play a role in the pathogenesis of the disease (Young et al. 2009).

**Phaeochromocytomas** tend to be benign and are a hallmark of Type 2 VHL syndrome. They appear mostly before the age of 40 years, and paediatric cases are common. They are catecholamine-producing neuroendocrine tumours or intra-adrenal paragangliomas, which are embryologically derived from the extra-adrenal chromaffin tissue; the same cells that give rise to the sympathetic nervous system. Germline mutations in the susceptibility genes responsible for hereditary phaeochromocytoma (*VHL, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, NF1*) can be detected in more than 25% of all cases and 40% of paediatric cases (Barontini and Dahia 2010).

**Pancreatic tumours** or cysts develop in 35–77% of VHL patients, most of the cysts being benign. Pancreatic tumours include cystadenomas (12%), haemangioblastomas (<1%), adenocarcinomas (<1%) and neuroendocrine tumours (9–17%). The mean age at diagnosis is 29–38 years. Malignant tumours occur in 8–50% patients and they can metastasise to the liver (Barontini and Dahia 2010).

**Endolymphatic sac tumours** are locally invasive papillary cystadenomas arising within the posterior temporal bone of the inner ear. Although they can occur sporadically, they are rare in the general population, but are frequently associated with VHL syndrome (Barontini and Dahia 2010).

**Papillary cystadenomas** arising from the epididymal duct are usually benign and occur in 25-60% of males with VHL syndrome, often in their teenage years. Papillary cystadenomas arising from the broad ligament in females is rare, thus the frequency and the age of usual onset is unknown. Both the epididymis in males and the broad ligament in females are derived from the embryonic mesonephric duct (Lonser et al 2003).

The AIHW National Hospital Morbidity Database (by principal diagnosis in ICD-10-AM) for 2007-2008 provides data on the number of hospital separations for disease types that would include VHL-associated neoplasms. It also provides data based on age group, which enables

the number of separations for patients of relevant age to be determined. However, the cause of the neoplasm is not defined and in many cases the specific disease is not differentiated ie haemangioblastomas are not separated from other benign neoplasms of the central nervous system. The total number of hospital separations for relevant principal diagnoses, and in the appropriate age groups is shown in Table 1.

Table 1  Number of hospital separations for disease types and specific age groups that would include VHL-associated neoplasms in Australia in 2007-2008

| Principle Diagnosis | Number of total separations | Age group-specific separations | |
|---|---|---|---|
| | | Separations | Age group |
| C64 Malignant kidney neoplasm | 3,980 | 1,264 | 20-59 years |
| D33 Benign neoplasms of the central nervous system | 551 | 79 | < 30 years |
| D31 Benign neoplasms of the eye and adnexia | 400 | 222 | < 30 years |
| D35.0 Benign neoplasms of the adrenal gland | 330 | 17 | < 20 years |
| D13.6 Benign neoplasms of the pancreas | 127 | 13 | 25-39 years |
| C25.4 Malignant neoplasm of endocrine pancreas | 33 | 2 | 25-39 years |
| D29.3 Benign neoplasms of the epididymus | 13 | 0 | 10-19 years |
| D28.2 Benign neoplasms of the uterine tubes and ligaments | 125 | | N/A |

## Description

VHL syndrome is an autosomal dominant neoplastic disease caused by germline mutations or deletions in one copy of the *VHL* tumour suppressor gene located on chromosome 3p25. The second copy of the *VHL* gene is fully functional. Tumours arise when spontaneous mutations occur in the second copy of the *VHL* gene in individual cells of affected organs. Most of the germline mutations are missense point mutations, but VHL syndrome can also be caused by deletion or truncation mutations of the *VHL* gene (Barontini & Dahia 2010). To date, detailed phenotype and gene mutation information is available for 945 VHL families (Nordstrom-O'Brien et al. 2010).

It is suggested that patients presenting with one or more characteristic lesions or a positive family history of VHL syndrome should be screened to determine if there is a germline mutation in the *VHL* gene. Currently, it is believed that genetic diagnostic techniques can detect virtually all cases of VHL syndrome (Barontini & Dahia 2010).

Direct sequencing of the polymerase chain reaction (PCR) amplified exons 1, 2 and 3 of the *VHL* gene remains the gold standard for detecting small germline gene mutations (Nordstrom-O'Brien et al. 2010). However, direct sequencing is not suitable for identification of partial and complete *VHL* gene deletions. Thus, multiplex ligation-dependent probe amplification (MLPA), which is based on the semi-quantitative PCR principle, is used to detect large deletions of the *VHL* gene.

Additionally, there is an association between genotype and phenotype that forms the basis of the clinical classification of VHL disease. Type 1 VHL disease does not include phaeochromocytoma, whereas phaeochromocytoma is a common feature of Type 2 disease. Type 2 disease can be further separated into three categories: Type 2A disease is associated with a low risk of renal cell carcinoma and pancreatic cysts. Type 2B has an increased risk of renal cancer and pancreatic cysts, and Type 2C is characterised by phaeochromocytoma only (Barontini & Dahia 2010).

The genetic defects of these subgroups are also distinct. Whereas, Type 2 disease is caused almost exclusively by missense mutations, Type 1 disease can result from deletions and truncations in addition to missense mutations. The mutant VHL protein in these subforms is believed to function differently, and may account for the clinical variability of the disease (Barontini & Dahia 2010). Knowing the type of VHL disease, could aid the medical practitioners in targeting screening towards the most likely manifestations of the disease in that patient.

## Administration, frequency of administration, and treatment

As the result is definitive, VHL genetic testing would only need to be performed once for each patient using duplicate sampling as recommended by The Royal College of Pathologists of Australasia in their 2007 position statement titled "Sample requirements for medical genetic testing: Do genetic tests demand a different standard?". However, two different types of delivery of VHL genetic tests would need to occur, namely:

**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 ie after the initial presentation, diagnosis, and treatment of the presenting complaint.

The presence of clinically relevant mutations in the *VHL* gene does not provide a diagnosis of the specific pathology; rather, this information indicates the likely presence of a VHL-associated neoplasm. Thus, when molecular testing is positive, it must be used in conjunction with routine screening in order to provide a disease-specific diagnosis. For this reason, the genetic test does not *diagnose* VHL syndrome, rather, it *predicts* a patient's risk of a future diagnosis of VHL syndrome.

It is proposed that the ordering of VHL genetic tests should be restricted to specialised genetic services, where appropriate genetic counselling may also be provided.

**Pre-symptomatic or predictive VHL genetic testing** would be performed as a non-urgent test once a VHL mutation has been identified in family members after accredited genetic counselling. Thus, it is suggested that the ordering of this test should be limited to specialised genetic services. The application suggested that presymptomatic testing should be

offered to first (mother, father or sibling) or second degree (grandparent, aunt, uncle, or half-sibling) family members and this protocol has been developed to reflect this[1] (Pathology Services Table Committee 2010).

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 relatives who have not inherited the family's VHL mutation, the genetic test would be a replacement for lifelong screening.

## Co-administered interventions

VHL syndrome is a progressive disease of diverse nature, with a high frequency of multiple neoplastic lesions in various organ systems. Thus, patients with VHL syndrome and first and second degree family members with *VHL* gene mutations require annual routine screening to detect new 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 confirmed VHL syndrome. However, a negative VHL genetic test will eliminate the requirement for annual screening. Thus, the test will replace the routine screening interventions for these patients.

The clinical diagnostic procedures used to monitor and detect specific VHL-associated neoplasms are described below.

**Haemangioblastomas** are diagnosed by magnetic resonance imaging (MRI) of the brain and the spinal cord. The clinical features of haemangioblastomas depend on the localisation of the tumours and are primarily due to their growth in the brain or spinal cord, and include headaches, numbness, dizziness, weakness or pain in the arms and legs, sensory deficits, gait or spinal ataxia, dysmetria, nystagmus, hydrocephalus and incontinence (Barontini & Dahia 2010).

Patients diagnosed with VHL syndrome and their first and second degree family members should have an MRI with gadolinium of the brain and spine every two years after the onset of puberty.

In their early stages, **retinal haemangioblastomas** are detectable only by examination of the dilated eye. Clinically, patients usually present with a painless loss of visual acuity or visual

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[1] Explicit confirmation is still being sought on whether the assessment will allow for the possibility of broadening indications wider than first and second degree relatives.

field or both. In advanced cases, they can present with haemorrhage, leading to secondary glaucoma and loss of vision. Peripheral retinal angioma is easily diagnosed by its typical fundoscopic aspect (Barontini & Dahia 2010).

Patients diagnosed with VHL syndrome and their first and second degree family members should have an annual eye/retinal examination with indirect ophthalmoscope by an ophthalmologist informed about the VHL history, and using a dilated examination.

**Clear-cell renal carcinomas** are the most common cause of death for patients with VHL syndrome. Renal cell carcinomas are detected using computed tomography (CT), MRI and ultrasound. Renal cell carcinomas often remain asymptomatic for a long time, thus diagnosis during pre-symptomatic screening is likely to improve patient outcomes. More advanced cases can present with haematuria, flank pain or a flank mass. Although renal cysts may be benign, they are considered premalignant lesions (Barontini & Dahia 2010).

**Pancreatic tumours** are detected by CT imaging. Patients rarely present with symptoms due to secreted peptides, like diarrhoea or hypoglycaemia, and most neuroendocrine tumours are non-functional and asymptomatic. However, these tumours can cause pancreatitis or pain (Barontini & Dahia 2010).

**Phaeochromocytomas** in VHL disease tend to be benign (less than 5% are malignant). In affected patients, hypertension is the most common symptom followed by headache and sweating. Other symptoms include palpitations, tachycardia, pallor and nausea. Nevertheless, when associated with VHL disease, about 30% of patients can be normotensive and asymptomatic. Phaeochromocytomas in VHL patients display a distinctly and consistently noradrenergic phenotype, with norepinephrine concentrations representing 98% and epinephrine concentrations only 1.5% of the total catecholamine content (Barontini & Dahia 2010).

The diagnosis is based on measuring the free metanephrine level in plasma. MRI, CT, [131] or [123]I(iodine)-methyl benzyl guanidine (MIBG) or octreotide scintigraphy, [18]F(fluoride)-DOPA-positron emission tomography (PET), ^{18}F-dopamine- and F-deoxyglucose scans are used for tumour localisation. Two imaging methods are necessary to document the tumour (Barontini & Dahia 2010).

Patients diagnosed with VHL syndrome and their first and second degree family members should have an annual ultrasound - of the abdomen with and without contrast - to assess their kidneys, pancreas, and adrenals, and the uterus in females. This should be replaced with a CT scan every two or three years. They should also have an annual blood test for elevated metanephrine levels.

**Endolymphatic sac tumours** are detected by MRI or CT. Clinical symptoms include hearing loss, tinnitus, vertigo or disequilibrium, aural fullness and, less frequently, facial paresis. The

hearing loss is irreversible. These tumours usually occur early in life with a mean age of onset of 22 years (Barontini & Dahia 2010). These symptoms are investigated as they occur, but are not screened for in Australia (expert advice of MESP clinical expert).

**Cystadenomas of the adnexal reproductive organs.** Epididymal cystadenomas in men are usually asymptomatic, are diagnosed by palpation and confirmed by ultrasound. Papillary cystadenomas arising from the broad ligament in females are diagnosed by CT or ultrasound. The tumours in both males and females are grossly and histologically alike (Lonser et al. 2003).

A summary of the screening procedures, divided by age, is provided in Table 2. This screening protocol is an adapted and simplified version of the VHL Family Alliance suggested screening guidelines for individuals at risk of VHL (VHL Family Alliance 2005).

Table 2  Australian VHL screening protocol

| Age | Screening Test |
|---|---|
| From Birth – 4 years | *Annually:*<br>- Eye review by ophthalmologist |
| Ages 5 - 14 | *Annually:*<br>- Eye review by ophthalmologist<br>- Medical specialist review: check of blood pressure, urine test or blood test to check for elevated catecholamines and metanephrines (phaeochromocytoma screen) |
| Age 15 and beyond | *Annually:*<br>- Eye review by ophthalmologist<br>- Medical specialist review: check of blood pressure, urine test or blood test to check for elevated catecholamines and metanephrines (phaeochromocytoma screen)<br>- Ultrasound of abdomen (kidneys, pancreas, and adrenals).<br>*Every 2 years*<br>- MRI with gadolinium of brain and entire spine cord (performed yearly if abnormality detected)<br>*Every 2-3 years*<br>- CT of abdomen (instead of that year's ultrasound) |

Source: advice from MESP clinical expert

A list of the Medicare Benefits Schedule (MBS) and Australian Refined Diagnosis Related Group (AR-DRG) numbers associated with these procedures are provided in Table 3.

**Table 3 Commonly occurring types of healthcare resources that are required to diagnose and monitor patients presenting with a neoplasm associated with VHL syndrome or with a family history of VHL syndrome**

| Type of resource and source | Identifier | Description | Quantity provided |
|---|---|---|---|
| Medicare Benefits Schedule (MBS) | MBS item number 23 | **LEVEL B CONSULTATION AT CONSULTING ROOMS** Professional attendance at consulting rooms by a general practitioner (not being a service to which any other item in this table applies) lasting less than 20 minutes, including any of the following that are clinically relevant: a) taking a patient history; b) performing a clinical examination; c) arranging any necessary investigation; d) implementing a management plan; e) providing appropriate preventive health care; in relation to 1 or more health-related issues, with appropriate documentation. | Fee: $34.90 Benefit: 100% = $34.90 |
| | MBS item number 104 | **SPECIALIST, REFERRED CONSULTATION - SURGERY OR HOSPITAL** (Professional attendance at consulting rooms or hospital by a specialist in the practice of his or her specialty where the patient is referred to him or her) **INITIAL** attendance in a single course of treatment, not being a service to which ophthalmology items 106, 109 or obstetric item 16401 apply. | Fee: $82.30 Benefit: 75% = $61.75 85% = $70.00 |
| | MBS item number 105 | Each attendance **SUBSEQUENT** to the first in a single course of treatment | Fee: $41.35 Benefit: 75% = $31.05 85% = $35.15 |
| | MBS item number 110 | **CONSULTANT PHYSICIAN (OTHER THAN IN PSYCHIATRY), REFERRED CONSULTATION - SURGERY OR HOSPITAL** (Professional attendance at consulting rooms or hospital by a consultant physician in the practice of his or her specialty (other than in psychiatry) where the patient is referred to him or her by a medical practitioner) - **INITIAL** attendance in a single course of treatment | Fee: $145.20 Benefit: 75% = $108.90 85% = $123.45 |
| | MBS item number 116 | - Each attendance (other than a service to which item 119 applies) **SUBSEQUENT** to the first in a single course of treatment | Fee: $72.65 Benefit: 75% = $54.50 85% = $61.80 |
| | MBS item number 132 | **CONSULTANT PHYSICIAN (OTHER THAN IN PSYCHIATRY) REFERRED PATIENT TREATMENT AND MANAGEMENT PLAN - SURGERY OR HOSPITAL** Professional attendance of at least 45 minutes duration for an initial assessment of a patient with at least two morbidities (this can include complex congenital, developmental and behavioural disorders), where the patient is referred by a medical practitioner, and where a) assessment is undertaken that covers: − a comprehensive history, including psychosocial history and medication review; − comprehensive multi or detailed single organ system assessment; − the formulation of differential diagnoses; and b) a consultant physician treatment and management plan of significant complexity is developed and provided to the referring practitioner that involves: − an opinion on diagnosis and risk assessment − treatment options and decisions − medication recommendations Not being an attendance on a patient in respect of whom, an attendance under items 110, 116 and 119 has been received on the same day by the same consultant physician. | Fee: $253.90 Benefit: 75% = $190.45 85% = $215.85 |

| | | | |
|---|---|---|---|
| | | Not being an attendance on the patient in respect of whom, in the preceding 12 months, payment has been made under this item for attendance by the same consultant physician. | |
| | MBS item number 133 | **CONSULTANT PHYSICIAN (OTHER THAN IN PSYCHIATRY) REVIEW OF REFERRED PATIENT TREATMENT AND MANAGEMENT PLAN - SURGERY OR HOSPITAL** Professional attendance of at least 20 minutes duration subsequent to the first attendance in a single course of treatment for a review of a patient with at least two morbidities (this can include complex congenital, developmental and behavioural disorders), where a) a review is undertaken that covers: − review of initial presenting problem/s and results of diagnostic investigations − review of responses to treatment and medication plans initiated at time of initial consultation comprehensive multi or detailed single organ system assessment, − review of original and differential diagnoses; and b) a modified consultant physician treatment and management plan is provided to the referring practitioner that involves, where appropriate: − a revised opinion on the diagnosis and risk assessment − treatment options and decisions − revised medication recommendations Not being an attendance on a patient in respect of whom, an attendance under item 110, 116 and 119 has been received on the same day by the same consultant physician. Being an attendance on a patient in respect of whom, in the preceding 12 months, payment has been made under item 132 by the same consultant physician, payable no more than twice in any 12 month period. | Fee: $127.10 Benefit: 75% = $95.35 85% = $108.05 |
| | MBS item number 66779 | **PATHOLOGY** Adrenaline, noradrenaline, dopamine, histamine, hydroxyindoleacetic acid (5HIAA), hydroxymethoxymandelic acid (HMMA), homovanillic acid (HVA), metanephrines, methoxyhydroxyphenylethylene glycol (MHPG), phenylacetic acid (PAA) or serotonin quantitation - 1 or more tests | Fee: $40.20 **Benefit:** 75% = $30.15 85% = $34.20 |
| | MBS item number 55036 | **ULTRASOUND SCAN OF ABDOMEN**, including scan of urinary tract when undertaken but not being a service associated with the service described in item 55600 or item 55603, where: (a) the patient is referred by a medical practitioner for ultrasonic examination not being a service associated with a service to which an item in Subgroups 2 or 3 of this Group applies; (b) the referring medical practitioner is not a member of a group of practitioners of which the providing practitioner is a member; and (c) the service is not performed with item 55038, 55044 or 55731 on the same patient within 24 hours (R) | Fee: $111.30 **Benefit:** 75% = $83.50 85% = $94.65 |
| | MBS item number 56407 | **COMPUTED TOMOGRAPHY** - scan of upper abdomen only (diaphragm to iliac crest) with intravenous contrast medium and with any scans of upper abdomen (diaphragm to iliac crest) prior to intravenous contrast injection, when undertaken, not being a service to which item 56307, 56507, 56807 or 57007 applies (R) (K) (Anaes.) | Fee: $360.00 **Benefit:** 75% = $270.00 85% = $306.00 |
| *(if abnormality detected on ultrasound)* | MBS item number 63111 | **MAGNETIC RESONANCE IMAGING** (including Magnetic Resonance Angiography if performed), performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by a specialist or by a consultant physician - **scan of head and cervical spine** for: - tumour of the central nervous system or meninges (R) (Contrast) (Anaes.) | Fee: $492.80 **Benefit:** 75% = $369.60 85% = $421.60 |

MBS = Medicare Benefits Schedule

## Background

## Current arrangements for public reimbursement

Currently, there is no MBS listing for any test that detects germline mutations in the *VHL* gene.

There are, however, MBS items that allow reimbursement for molecular tests that detect specific genetic mutations (Table 4). The range of MBS fees associated with these items is indicative of the range of molecular methodologies used to detect the relevant mutations. Quantitative or semi-quantitative assays will incur greater costs than methods that are simply qualitative.

Table 4  Current MBS items related to detection of genetic mutations

| Item 73308 | Characterisation of the genotype of a patient for Factor V Leiden gene mutation, or detection of the other relevant mutations in the investigation of proven venous thrombosis or pulmonary embolism - 1 or more tests <br> Fee: $36.70 |
|---|---|
| Item 73311 | Characterisation of the genotype of a person who is a first degree relative of a person who has proven to have 1 or more abnormal <br> genotypes under item 73308 - 1 or more tests <br> Fee: $36.70 |
| Item 73317 | Detection of the C282Y genetic mutation of the HFE gene and, if performed, detection of other mutations for haemochromatosis where: <br> (a) the patient has an elevated transferrin saturation or elevated serum ferritin on testing of repeated specimens; or <br> (b) the patient has a first degree relative with haemochromatosis; or <br> (c) the patient has a first degree relative with homozygosity for the C282Y genetic mutation, or with compound heterozygosity for recognised genetic mutations for haemochromatosis <br> (Item is subject to rule 20) <br> Fee: $36.70 |
| Item 73320 | Detection of HLA-B27 by nucleic acid amplification includes a service described in 71147 unless the service in item 73320 is rendered as a pathologist determinable service. <br> (Item is subject to rule 27) <br> Fee: $40.80 |
| Item 73305 | Detection of genetic mutation of the FMR1 gene by Southern Blot where the results in item 73300 are inconclusive <br> Fee: $204.00 |
| Item 73314 | Characterisation of gene rearrangement or the identification of mutations within a known gene rearrangement, in the diagnosis and monitoring of patients with laboratory evidence of: <br> (a) acute myeloid leukaemia; or <br> (b) acute promyelocytic leukaemia; or <br> (c) acute lymphoid leukaemia; or <br> (d) chronic myeloid leukaemia; <br> Fee: $232.50 |

Source: (Department of Health and Ageing 2009)

Currently, the Royal College of Pathologists of Australasia genetic testing website lists only two pathology laboratories that offer VHL genetic testing, using assays developed in house, and

they offer two different levels of service. The Cancer Genetics Diagnostic Laboratory, PaLMS-RNSH in NSW, offer DNA sequencing of all 3 exons of the *VHL* gene with a turnaround time of 3 months. This test detects point mutations and frame-shift mutations but not large deletion mutations, and therefore does not identify all patients with VHL syndrome. On the other hand, the Molecular Pathology Division of the Institute of Medical and Veterinary Science (IMVS), Adelaide, SA, offers both DNA sequencing and MLPA analysis of the *VHL* gene for patients referred through a clinical genetic service with a turnaround time of 2 months for A$600. This enables the detection of point mutations, frame-shift mutations and large deletions of *VHL* gene, and identifies virtually all cases of VHL syndrome.

Diagnostic VHL genetic testing is also commercially available. A Swiss company (Diagnogene) offers DNA sequencing for approximately A$687. However, this does not include analysis for gene deletions (MLPA). A Belgian firm, GenDia, offers both sequencing and MLPA analysis for around A$1,223. Predictive testing is cheaper than diagnostic testing as laboratories are identifying a *specific* abnormality in family members that was first identified in the index case. The cost through Diagnogene is not known. GenDia charge approximately A$440. The IMVS charge $340 for predictive testing.

As the national demand for VHL testing is likely to be low, VHL genetic testing is likely to be undertaken by a small number of laboratories so as to ensure that they have sufficient throughput to maintain training and procedural quality.

Testing of the *VHL* gene can be completed using conventional methods and instrumentation in a genetic pathology laboratory. The staffing required will depend on the caseload, throughput, and infrastructure of the laboratories which provide testing.

## Regulatory status

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 the same level of regulatory scrutiny as commercial kits. As testing for VHL is currently only provided as an in-house IVD, it would be classified as a Class 3 in-house IVD (see Box 1).

Box 1    Classification of Class 3 in vitro diagnostic 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/ivd/ivd-classification.htm [accessed January 2011]

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 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. Manufacturers of Class 2, Class 3 and Class 4 IVDs must hold certification from a regulatory body to show compliance with a suitable conformity assessment procedure (Therapeutic Goods Administration 2009).

## Patient Population

### Clinical place for proposed intervention

It is suggested that diagnostic VHL genetic testing will allow patients presenting with a clinical feature suggestive of VHL to be definitively diagnosed. Currently, the possibility of misdiagnosis is relatively high. In an Italian study, 14 patients with haemangioblastomas of the central nervous system were surgically treated to remove the lesion then clinically

screened for the presence of VHL disease (Catapano et al. 2005). On the basis of clinical screening alone, all were classified as not having VHL disease. The patients then agreed to genetic screening, and a germline mutation of the *VHL* gene was identified in two patients; a false negative rate of 14%. Other studies have reported false negative rates of 4-10% (Hes & Feldberg 1999; Oberstraß et al. 1996; Olschwang et al. 1998). The sensitivity and specificity of the VHL genetic test is reported to be up to 99% (Hes & Feldberg 1999), although this has yet to be confirmed by the planned systematic review.

After treatment for the presenting complaint, those patients a clinical or genetic diagnosis of VHL would still receive lifelong routine screening for early detection of new neoplasms, however knowledge of the VHL disease subtype may allow medical practitioners to streamline patient management to screen more rigorously for the neoplasms that are most likely to develop as a consequence of that subtype. For example, a patient with Type 1 VHL disease will not develop a phaeochromocytoma, whereas a patient with Type 2C VHL disease is unlikely to develop any neoplasma except a phaeochromocytoma. Those symptomatic patients with suspected VHL, who are actually negative for a VHL mutation (assuming testing is accurate), would avoid lifelong screening for new neoplasms. The VHL genetic test would be used in *addition* to clinical diagnosis but would act as a triage test for ongoing surveillance.

Predictive VHL genetic testing would also allow triaging of first and second degree family members of patients with confirmed mutations in the *VHL* gene; providing a mechanism for identifying the individuals that require lifelong routine screening. Those who do not have the mutation do not need to undergo unnecessary lifelong screening procedures, and those that do have the mutation can receive screening targeted according to their VHL disease subtype. This will benefit individual family members, as the psychological burden for those not affected can be eased, and those that inherited the condition can use routine screening to ensure early detection and prompt treatment of any neoplasms that develop. It will also have an impact on hospital resources, as only those family members that have actually inherited *VHL* gene mutations will be screened routinely.

There will be a very small number of patients who receive a negative *VHL* gene test despite having a range of VHL type tumours, who may have somatic genetic mosaicism. Genetic mosaicism occurs when the somatic cells of an individual are of more than one distinct genotype (De 2011). It is therefore possible to have a genetic mutation within cells of one part of the body, resulting in VHL syndrome, which is undetectable by testing the peripheral blood supply. These patients would still require lifelong monitoring, and their close family members would require screening. The real incidence of somatic mosaicism in VHL patients is unclear (Santarpia et al. 2007).

In one study conducted in Mexico City, a germline *VHL* gene mutation was identified in 12 families and genetic testing offered to family members at 25-50% risk of having the mutation; 60% agreed to be tested (Rasmussen et al. 2010). Of those family members that were tested,

74% did not inherit the *VHL* gene mutation and required no further screening. The remaining 26% were offered routine screening, however only 40% of these patients continued annual screening after five years. Therefore, compliance with ongoing surveillance, irrespective of VHL mutation status, may have an impact on any savings realised by accurately determining an individual's risk of disease.

In Australians with familial cancer, there are approximately 11.5 first and second degree relatives per patient with a documented heritable mutation. Of these, approximately 40% take up the offer of pre-symptomatic genetic testing (Pathology Services Table Committee 2010).

A management algorithm is provided below for both the diagnostic and predictive use of VHL genetic testing (Figure 1). The left side explains the approach to the diagnosis and prediction of VHL syndrome in a setting without genetic testing (assumed to be the current approach for the sake of simplicity, 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 white text boxes and solid lines relate to the diagnosis and treatment of people with clinical features suggestive of having VHL syndrome, while the black boxes and dashes correspond to the management of their close family members. The arrow relevant to patients with somatic mosaicism has been lightened to lessen the emphasis of this pathway, due to the rarity of occurrence.

Special emphasis should be given to material differences between the management algorithms outlining "current" and "proposed" clinical management of VHL syndrome in the type of healthcare resources and the frequencies of their use. The main difference between the algorithms is the targeted use of life-long surveillance in patients and family members that have a definitive diagnosis of VHL syndrome (due to having the mutation), and fewer patients overlooked for surveillance due to a negative misdiagnosis (false negative). If VHL syndrome is diagnosed, patients and family members with VHL gene mutations will require a life-long management plan involving annual screening - these resources are listed in Table 3.

Figure 1    Management algorithm for use of VHL genetic testing in patients that present with clinical features suggestive of VHL syndrome as well as their 1st and 2nd degree relatives

Patients presenting with one or more clinical features suggestive of VHL syndrome:
Haemangioblastomas of the retina or CNS, or phaeochromocytomas

Treatment of presenting complaint[a] or monitoring of incident neoplasm

*Current pathway*                                    *Proposed pathway*

Continued monitoring of incident neoplasm/ no further follow-up

-ve

Clinical testing for VHL syndrome[b]

Clinical testing for VHL syndrome[b] plus genetic counselling and testing for VHL mutation

-ve for syndrome AND mutation

Continued monitoring of incident neoplasm/ no further follow-up

+ve for syndrome AND -ve for mutation (somatic mosaicism)

+ve OR -ve for syndrome AND +ve for mutation

1st or 2nd degree relatives do not require testing for VHL mutations or monitoring for VHL syndrome

+ve

1st or 2nd degree relatives do not require monitoring for VHL syndrome

Treatment of any other neoplasms detected[a] and / or continued monitoring of incident neoplasm

Genetic counselling and testing in 1st and 2nd degree relatives for familial VHL mutation

-ve

No further follow-up

+ve

1st and 2nd degree relatives receive clinical testing and routine lifelong screening to identify neoplasms[b]

Routine lifelong screening to identify new neoplasms[b]

1st and 2nd degree relatives receive clinical testing and routine lifelong screening to identify neoplasms[b]

Early detection of neoplasms, treatment as required, and continued screening[b]

Early detection of neoplasms, treatment as required, and continued screening[b]

Early detection of neoplasms, treatment as required, and continued screening[b]

Outcomes

Direct effectiveness :    Primary  = mortality, overall/progression-free survival, quality of life, incidence and severity of life-threatening events
                          Secondary = incidence of symptoms, cancer detection rates, tumour stage, age at diagnosis
Predictive accuracy:      Sensitivity and specificity (and therefore rates of false positives and negatives), positive and negative likelihood ratios, positive and negative predictive values (and therefore false alarm and reassurance rates), diagnostic odds ratios, receiver operator characteristic curves, area under the curve, accuracy
Change in management :    Rate and type of referral, frequency and compliance with clinical screening, rate and type of treatment, hospital separations and re-admissions, length of hospital stay
Safety:                   Psychological and physical harms from testing and clinical screening

Notes:
1st degree relatives are parents, offspring and siblings that share 50% of their genes; 2nd degree relatives are grandparents, grandchildren, uncle, auntie, nephew, niece, half-sibling that share 25% of their genes
[a] Surgical resection, radiotherapy, laser therapy, anti-VEGF therapy; [b]Clinical testing = CT, MRI, ultrasound, urine and blood tests, family history, clinical history, other tests as appropriate to identify any signs of disease other than presenting complaint; biopsy and histopathology of any neoplasms; [c]Screening = CT, MRI, ultrasound, urine and blood tests; CNS=central nervous system

## Proposed MBS listing

Based on the predicted patient population and the proposed intervention, the proposed MBS items are suggested as:

1. A diagnostic test to detect germline mutations in the *VHL* gene
2. A predictive test to detect mutations in the *VHL* gene in family members of a proband.

The proposed MBS items are summarised in Table 5. The ordering of these tests should be restricted to specialised genetic services. 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.

Table 5    Proposed MBS item descriptor for VHL genetic testing

| |
|---|
| Category 6–Pathology services |
| MBS [item number 1] |
| Detection of germline mutations of the *VHL* gene in: |
| (a)  Patients with a clinical diagnosis of VHL syndrome: |
| -   Family history of VHL, and a haemangioblastoma (retinal or CNS), phaeochromocytoma, or clear cell renal carcinoma ; or |
| -   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) |
| (b)  Or 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 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 by a clinical geneticist on referral. Further counselling may be necessary upon receipt of the test results. |
| MBS [item number 2] |
| Detection of germline mutations of the *VHL* gene in: |
| (a)  Biological relatives of patients with a known mutation in the *VHL* gene |
| Fee: $340 |
| Prior to ordering these tests the ordering practitioner should ensure 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 by a clinical geneticist on referral. Further counselling may be necessary upon receipt of the test results. |

## Comparator

Diagnosis of VHL syndrome is currently based on clinical criteria. Patients with a family history, and a haemangioblastoma (including retinal haemangioblastomas), phaeochromocytoma, or clear cell renal 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 (Nordstrom-O'Brien et al. 2010).

The healthcare resources that are 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, and are listed in Table 3. Only family members with no pathogenic mutations in the *VHL* gene do not require clinical screening.

The resources required to treat patients presenting with a VHL-associated neoplasm are basically the same regardless of the methods of diagnosis, and therefore the costs associated with treatment will be excluded from consideration from this assessment.

## Outcomes[2]

The health outcomes, upon which the comparative clinical performance of VHL genetic testing (in addition to current VHL diagnostic approaches) versus the comparator of current VHL diagnostic approaches alone will be measured, are:

### Effectiveness

*Primary (patient relevant)*

- mortality

- overall/progression-free survival

- quality of life

- incidence and severity of life-threatening events arising from complications due to haemangioblastomas of the central nervous system, clear-cell renal cell carcinomas, and other malignant neoplasms associated with VHL syndrome

*Secondary*

- incidence of symptoms arising from haemangioblastomas of the retina and central nervous system, endolymphatic sac tumours, phaeochromocytomas, renal cysts and clear-cell renal cell

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[2] These will be assessed in the event that there is direct evidence of the effect of genetic testing on health outcomes (eg randomised controlled trials or intervention studies). In the absence of this evidence, a linked evidence approach will be used – the PICO criteria that are relevant to this type of evidence are given in Appendix A.

carcinomas, pancreatic cysts and tumours, and cystadenomas of the adnexal reproductive organs

- cancer detection rates

- age at diagnosis

*Safety*

- psychological and physical harms from genetic testing and clinical screening

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

Table 6 provides a summary of the PICO used to:

(1) define the question for public funding,

(2) select the direct evidence assessing the safety and effectiveness of genetic testing for VHL mutations, and

(3) provide the systematically acquired evidence-based inputs (transition probabilities) for any decision-analytic modelling to determine the cost-effectiveness of genetic testing for VHL mutations.

The methodology for undertaking this evidence-based assessment of genetic testing in the diagnosis of VHL syndrome is outlined in detail in the "Assessment methodology" section of the protocol.

**Table 6 Summary of PICO to define research questions that the assessment will investigate**

| Patients | Intervention | Comparator | Reference Standard | Outcomes to be assessed |
|---|---|---|---|---|
| Patients presenting with one or more clinical features suggestive of VHL syndrome. | VHL genetic testing using DNA sequencing, and MLPA to diagnose *VHL* gene mutations **and** clinical diagnosis from family history, clinical history, tests including CT, MRI, ultrasound, hearing test, eye exam, blood tests, other tests as appropriate to identify any signs of disease other than presenting complaint | Clinical diagnosis from family history, clinical history, tests including: CT, MRI, ultrasound, hearing test, eye exam, blood tests, other tests as appropriate to identify any signs of disease other than presenting complaint | Clinical diagnosis determined from long term follow-up | **Safety**<br>Psychological and physical harms from genetic testing and clinical screening<br>**Effectiveness**<br>*Direct evidence*<br>Primary outcomes – mortality/survival, progression-free survival, quality of life, incidence and severity of life-threatening events arising from complications due to haemangioblastomas of the central nervous system, clear-cell renal cell carcinomas, and other malignant neoplasms associated with VHL syndrome<br>Secondary outcomes - incidence and severity of symptoms (arising from haemangioblastomas of the retina and central nervous system, endolymphatic sac tumours, phaeochromocytomas, renal cysts and clear-cell renal cell carcinomas, pancreatic cysts and tumours, and cystadenomas of the adnexal reproductive organs), age at diagnosis<br>*Plus linked evidence [a]* |
| Clinically unaffected first or second degree family members of patients with clinically diagnosed VHL syndrome and/or a diagnosed VHL genetic abnormality. | VHL genetic testing to screen for *VHL* gene mutations ± clinical testing (CT, MRI, ultrasound, hearing test, eye exam, and blood tests) **and** routine lifelong screening for neoplasms using CT, MRI, ultrasound, hearing test, eye exam, and blood tests | Clinical testing (CT, MRI, ultrasound, hearing test, eye exam, and blood tests)<br>**and** routine lifelong screening for neoplasms using CT, MRI, ultrasound, hearing test, eye exam, and blood tests | Clinical diagnosis determined from long term follow-up | **Safety**<br>Psychological and physical harms from genetic testing and clinical screening<br>**Effectiveness**<br>*Direct evidence*<br>Primary outcomes – mortality/survival, progression-free survival, quality of life, incidence and severity of life-threatening events arising from complications due to haemangioblastomas of the central nervous system, clear-cell renal cell carcinomas, and other malignant neoplasms associated with VHL syndrome<br>Secondary outcomes - incidence of symptoms (arising from haemangioblastomas of the retina and central nervous system, endolymphatic sac tumours, phaeochromocytomas, renal cysts and clear-cell renal cell carcinomas, pancreatic cysts and tumours, and cystadenomas of the adnexal reproductive organs), age at diagnosis, *Plus linked evidence [a]* |

**Research Questions**

1. *Is VHL genetic testing safe and effective when used as an addition to clinical diagnostic approaches in the diagnosis of patients presenting with symptoms suggestive of VHL syndrome?*
2. *Is VHL genetic testing safe and effective when used as a triage test for life-long screening of family members of patients who are positive for a VHL mutation?*

[a] See Appendix A.

## Clinical claim

The PSTC application claims that: (i) VHL genetic testing ensures identification of all patients with VHL syndrome so lifelong routine screening can be accurately targeted to enable early detection and treatment of any new neoplasms that develop; and (ii) VHL genetic testing ensures identification of all family members with VHL syndrome so lifelong routine screening and treatment can be provided, and unnecessary screening of family members that have not inherited the condition can be avoided.

These claims suggest that genetic testing (i) as an addition to current diagnostic approaches to identify VHL syndrome in patients; and (ii) as a triage test for the screening of family members of a patient with confirmed VHL syndrome, would result in superior health outcomes for those symptomatic individuals who previously had a false negative clinical diagnosis and receive a true positive genetic diagnosis, as well as for family members that have a negative genetic diagnosis.

Relative to the comparator, VHL genetic testing would therefore be considered non-inferior in terms of safety and superior in terms of overall effectiveness. As such, the type of economic evaluation required is a cost-effectiveness analysis or cost-utility analysis (green shading in Table 7). Should superiority in health outcomes be unable to be demonstrated due to a lack of evidence, it would need to be demonstrated that comparative effectiveness and safety was no worse as a consequence of replacing current diagnostic/predictive approaches with molecular testing and a cost-minimisation or simple cost comparison analysis conducted, with appropriate exploration of the degree of uncertainty associated with the assumption of non-inferiority (orange shading in Table 7).

Table 7  Classification of an intervention for determination of economic evaluation

| | | Comparative effectiveness versus comparator | | | | |
|---|---|---|---|---|---|---|
| | | Superior | | Non-inferior | Inferior | |
| Comparative safety versus comparator | Superior | CEA/CUA | | CEA/CUA | Net clinical benefit | CEA/CUA |
| | | | | | Neutral benefit | CEA/CUA* |
| | | | | | Net harms | None^ |
| | Non-inferior | CEA/CUA | | CEA/CUA* | None^ | |
| | Inferior | Net clinical benefit | CEA/CUA | None^ | None^ | |
| | | Neutral benefit | CEA/CUA* | | | |
| | | Net harms | None^ | | | |

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

It is likely that the greatest cost saving for VHL genetic testing would be among the family members of patients with VHL syndrome because unnecessary screening of family members that

have not inherited the condition can be avoided. The cost of yearly ophthalmologic and catecholamine screening was US$650 (excluding time lost from work) in 1998, compared to US$260 for direct sequencing of the *VHL* gene. The cost over a 20-year screening period would be US$13,000; a saving of over US$12,000 per VHL-negative person. If costs for screening procedures such as magnetic resonance imaging (MRI) of the brain, the spinal canal and abdomen are added, the cost savings can increase substantially (Ho, Banerjee & Mensinkai 2003).

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

### Outcomes for economic evaluation

Ideally the health outcomes used in the economic evaluation are life-years gained and/or quality-adjusted life-years gained. However, these outcomes might not be able to be determined from the usual published evidence available for a diagnostic or predictive test. In the case where data on these primary outcomes are not available, it may be possible to use secondary outcomes as an alternative.

As stated previously, the health outcomes - upon which the comparative clinical performance of genetic testing for VHL syndrome in addition to current VHL syndrome diagnostic approaches versus the comparator (current VHL diagnostic approaches alone) will be measured - are:

*Effectiveness*

*Primary (patient relevant)*

- mortality

- overall/progression-free survival

- quality of life

- incidence and severity of life-threatening events arising from complications due to haemangioblastomas of the central nervous system, clear-cell renal cell carcinomas, and other malignant neoplasms associated with VHL syndrome

*Secondary*

- incidence and severity of symptoms arising from haemangioblastomas of the retina and central nervous system, endolymphatic sac tumours, phaeochromocytomas, renal cysts and clear-cell renal cell carcinomas, pancreatic cysts and tumours, and cystadenomas of the adnexal reproductive organs

- cancer detection rates, age at diagnosis, predictive accuracy outcomes (See Appendix A for outcomes from a linked evidence approach), rates of referral, type of referral, frequency and compliance with clinical screening, rate and type of treatment, hospital separations and re-admissions, hospital length of stay

## Health care resources

Given that the proposed genetic testing will be used in addition to current clinical testing in the diagnosis of VHL syndrome, the cost of initial clinical testing will not be considered in the economic evaluation. For VHL prediction testing, one genetic test will replace lifelong surveillance for those that test negative to the VHL mutation. The main types of costs associated with an economic evaluation are the cost of genetic testing, and the cost of lifelong screening.

Patients in different age groups will receive different screening tests, thus the costs of lifelong screening will vary according to age. Clinical advice will be used to estimate the proportion of patients and their family members in each age group. The table below, including the disaggregated unit costs, will be completed during the assessment.

**Table 8 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 in association with clinical assessment and lifelong screening | | | | | | | | | | |
| - eye/retinal exam | ophthalmologist | outpatient | Clinical advice | Annually, Clinical advice | Item 104 ($82.30) Item 109 ($123.65) | | | | | |
| - Physical/ neurological assessment | Physician/ paediatrician | outpatient | Clinical advice | Annually | Item 104 ($82.30) | | | | | |
| - Urine or blood sample test | pathologist | outpatient | Clinical advice | Clinical advice | Item 66779 ($40.20) | | | | | |
| - Abdominal ultrasonography | radiologist | outpatient | Clinical advice | Annually (from 8 years) | Item 55036 ($111.30) | | | | | |
| - MRI with gadolinium of brain and spine | radiologist | outpatient | Clinical advice | Clinical advice | Item 63111 ($492.8) | | | | | |
| - CT scan of abdomen | radiologist | outpatient | Clinical advice | Clinical advice | Item 56407 ($360) | | | | | |
| - Abdominal MRI | radiologist | outpatient | Clinical advice | Clinical advice | Item 63482 ($403.20) | | | | | |
| Resources provided to deliver proposed genetic testing | | | | | | | | | | |
| - Genetic counselling | Specialist physician/ geneticist | outpatient | 100% | once lifetime once lifetime | Item 132 ($253.90) Item 133 ($127.10) | | | | | |
| - Genetic diagnostic testing | Specialist physician/ geneticist | outpatient | 100% | once lifetime | Proposed fee $600 | | | | | |
| - Genetic predictive testing | Specialist physician/ geneticist | outpatient | 100% | once lifetime | Proposed fee $340 | | | | | |
| - Genetic predictive testing when VHL mutation unknown | Specialist physician/ geneticist | outpatient | 100% | once lifetime | Proposed fee $600 | | | | | |

## Proposed structure of economic evaluation (decision-analytic)

The extended PICO to be used for the economic evaluation are provided in Table 9.

Table 9  Summary of extended PICO to define research questions that economic evaluation will investigate

| Patients | Intervention | Comparator | Outcomes to be assessed | Healthcare resources to be considered |
|---|---|---|---|---|
| Patients presenting with one or more clinical features suggestive of VHL syndrome. | VHL genetic testing using DNA sequencing, and MLPA to diagnose *VHL* gene mutations **and** clinical diagnosis from family history, clinical history, tests including CT, MRI, ultrasound, hearing test, eye exam, blood tests, other tests as appropriate to identify any signs of disease other than presenting complaint | Clinical diagnosis from family history, clinical history, tests including: CT, MRI, ultrasound, hearing test, eye exam, blood tests, other tests as appropriate to identify any signs of disease other than presenting complaint | <u>Safety</u><br>Psychological and physical harms from testing<br><u>Effectiveness</u><br>*Direct evidence*<br>Primary outcomes – see Table 6<br>Secondary outcomes – see Table 6<br><br>*Linked evidence [a]*<br><br><u>Cost-effectiveness outcomes</u> | See Table 8 |
| Clinically unaffected first or second degree family members of patients with a diagnosed VHL genetic abnormality. | VHL genetic testing to screen for *VHL* gene mutations ± clinical testing (CT, MRI, ultrasound, hearing test, eye exam, and blood tests) **and** routine lifelong screening for neoplasms using CT, MRI, ultrasound, hearing test, eye exam, and blood tests | Clinical testing (CT, MRI, ultrasound, hearing test, eye exam, and blood tests)<br>**and** routine lifelong screening for neoplasms using CT, MRI, ultrasound, hearing test, eye exam, and blood tests | <u>Safety</u><br>Psychological and physical harms from testing<br><u>Effectiveness</u><br>*Direct evidence*<br>Primary outcomes – see Table 6<br>Secondary outcomes – see Table 6<br><br>*Linked evidence [a]*<br><br><u>Cost-effectiveness outcomes</u> | See Table 8 |

<u>Research Questions</u>

1. *Is VHL genetic testing cost-effective when used in addition to clinical diagnostic approaches in the diagnosis of patients presenting with symptoms suggestive of VHL syndrome?*
2. *Is VHL genetic testing cost-effective when used as a triage test for life-long screening of family members of patients who are clinically diagnosed with VHL syndrome and/or positive for a VHL mutation?*

[a] See Appendix A for outcomes if a linked evidence approach is needed.

Cost-effectiveness outcomes have been included in Table 9 so that literature on economic models and trial-based economic evaluations published in the peer-reviewed literature can be canvassed. Their applicability to the Australian health system is, however, likely to be limited and so their utility is primarily to inform the decision-analytic modelling that will be conducted according to the perspective of the Australian health system.

Figure 1 and 3 outline the decision analytics that will be used when modelling the cost-effectiveness of the two proposed scenarios for the usage of genetic testing for VHL ie when

genetic testing is used for diagnosis alone (Figure 2) and when it is used for diagnosis of the proband, and then prediction of VHL within associated family members (Figure 3). The predictive setting alone will not be presented, as relatives are only tested for a known mutation, once a specific mutation has been identified in the proband (index case). Figure 3 shows the decision tree appropriate for when index cases and first degree relatives are assessed. A subsequent stepped analysis will be conducted assessing the cost-effectiveness of broadening the funding of genetic testing to include second degree relatives as well. This analysis would include the proportion of relatives expected to be first and second degree, as well as incorporate their respective probabilities of having the mutation.

PASC has advised that there is unlikely to be any treatment change resulting from the introduction of genetic testing for VHL.  Therefore there is not expected to be any health benefit resulting from genetic testing. If during the literature review, direct evidence *is* available, the decision trees will be expanded to include treatment and corresponding health outcomes.

**Figure 2** Decision tree representing the decision options of using VHL genetic testing for the diagnosis of VHL syndrome (MBS item 1)



CT = clinical testing
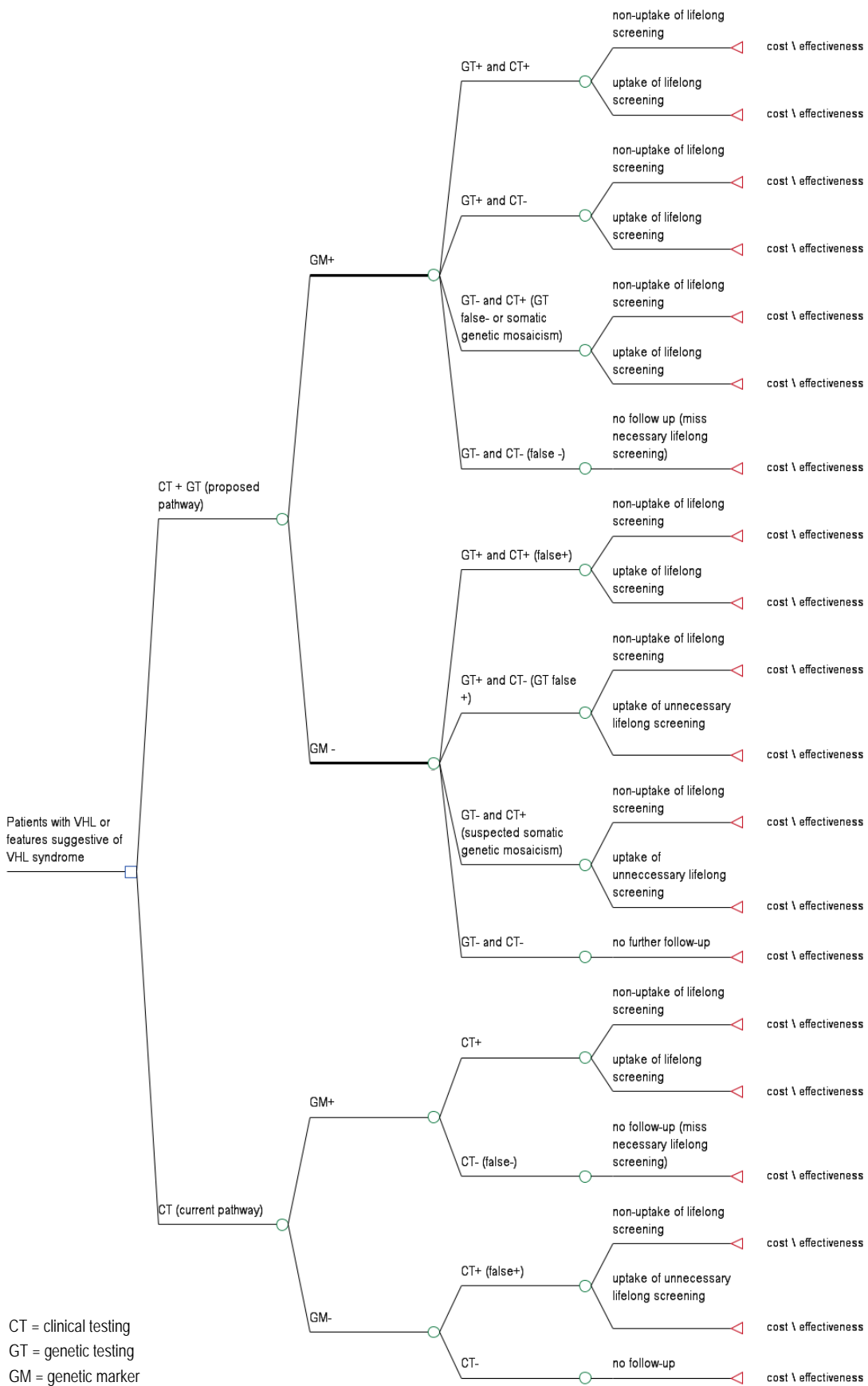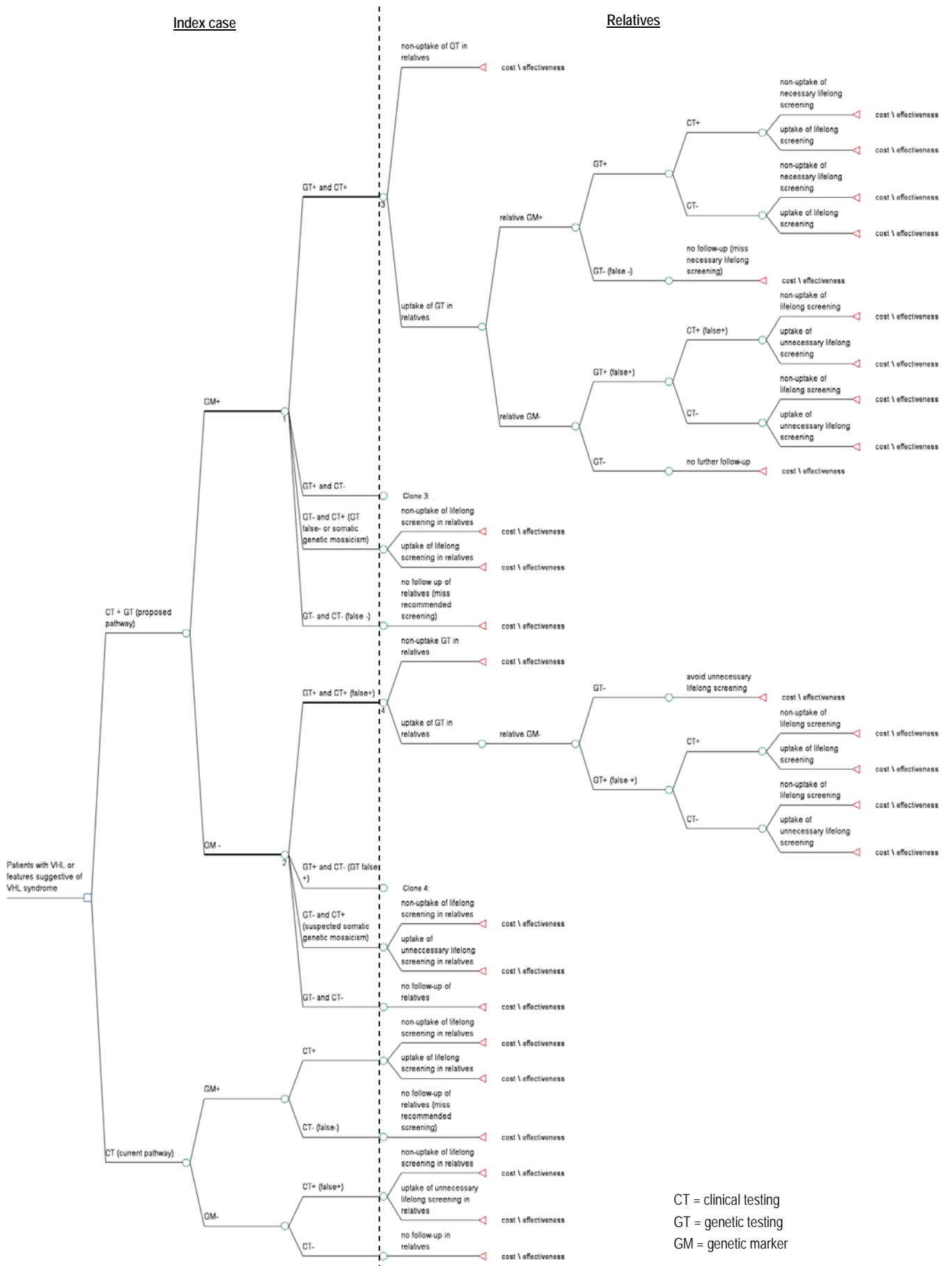GT = genetic testing
GM = genetic marker

**Figure 3** Decision tree representing the decision options of using VHL genetic testing for the prediction of VHL syndrome in family members of a patient with a known mutation (MBS items 2)



CT = clinical testing
GT = genetic testing
GM = genetic marker

## Assessment methodology

Clinical need for VHL genetic testing in Australia will be determined using available national data collections such as the AIHW National Hospital Morbidity and Mortality Database, as well as published literature concerning the incidence and prevalence of the condition.

A systematic literature review will then be undertaken to assess the safety and effectiveness of VHL genetic testing in (1) symptomatic patients with suspected VHL syndrome, and (2) clinically unaffected first or second degree family members of individuals with a VHL mutation. A systematic literature review is undertaken because it is a method that is transparent and reduces bias in the selection and reporting of pertinent evidence. This review of evidence will then be used to provide the inputs and derive the transition probabilities needed for the decision-analytic model to determine the cost-effectiveness of the use of VHL genetic testing in each of the two funding scenarios.

The effectiveness of a diagnostic test depends on whether it improves patient health outcomes. This can be assessed by studies that directly investigate the impact of the test on health outcomes or alternatively, in some situations, by linking evidence from studies.

Should there be no direct evidence (eg clinical trials) available assessing the impact of VHL genetic testing on patient outcomes, either for screening or for diagnosis in a population with presenting symptoms, a linked evidence approach will be undertaken using the methods outlined in the MSAC (2005) *Guidelines for the assessment of diagnostic technologies*.

A linked evidence approach involves narratively linking evidence reporting on three aspects of a diagnostic test intervention, if certain conditions are met. These aspects are:

test accuracy - measured for example, by sensitivity, specificity, positive or negative predictive values or likelihood ratios. This involves comparing the VHL genetic test results against a reference standard ('truth'). This reference standard is the clinical diagnosis based on all available information including clinical outcome over long-term follow-up;

impact on clinical decision making - measured as the change in treatment decision made by clinicians in response to the information provided by the VHL genetic test; and

effectiveness of treatment – measured as the impact of the change in management, based on the genetic test, on the health outcomes of those people diagnosed with VHL syndrome. However, it is expected that there would be no change in treatment for patients with VHL. Likewise for family members, although there is likely to be a change in the rate of routine screening (as those who are *VHL* mutation negative may avoid screening), there is unlikely to be any *treatment* change. Therefore the effectiveness of change in treatment need not be assessed.

Information provided from a linked evidence approach feeds directly into the development of decision analytic models. However, because the approach is pre-specified and there are criteria for selecting the evidence, it means that the model (and model results) is less likely to be open to bias and the inputs are the best available evidence that is applicable to the question for public funding. Further, the full range of possible results is provided in the evidence-base so that uncertainty can be explored within a known range. In instances where the test will not affect the type of treatment a patient would receive, or if treatment is not likely to be received any earlier than currently, then the linkage to assess the effect of treatment on patient health outcomes may not be necessary. Clinical advice suggests that assessment of treatment effectiveness is not necessary for patients with VHL syndrome as VHL genetic testing is unlikely to affect treatment received or the treatment outcomes. Any cost-effectiveness analysis would simply be reduced to the incremental cost per correct diagnosis.

## Literature search

An initial search will be conducted to identify any existing health technology assessment (HTA) reports on VHL genetic testing. The electronic databases and websites of international HTA agencies are found in Appendix B.

Search strategies are generally developed using the key elements of the research question, outlined in Table 6 and Table 9. Table 10 outlines the search terms for this review, based on an Embase.com search platform and initial searching for direct evidence of effectiveness and safety of diagnostic testing for VHL. Should direct evidence be unavailable, the same search terms will be used to search for literature on the predictive accuracy and change in management studies appropriate for linked evidence (see Appendix A).

Appendix C lists the databases and websites that will be searched for appropriate literature.

**Table 10        Search terms for VHL genetic testing (direct evidence)**

| Element of clinical question | Suggested search terms |
|---|---|
| Population | 'von hippel lindau disease'/exp OR 'von hippel lindau' OR 'vhl' OR 'vhl gene' OR 'vhl mutation' |
| Intervention/test | AND<br>'genetic screening'/exp OR 'genetic screening' OR 'genetic test' OR 'genetic testing' OR 'molecular test' OR 'molecular testing' OR 'DNA screening'/exp OR 'DNA screening' OR 'DNA test' OR 'DNA testing' OR 'sequence analysis'/exp OR 'sequence analysis' OR 'genetic procedures'/exp OR 'genetic procedure' OR 'molecular pathology'/exp OR 'gene sequencing' OR 'molecular diagnosis' OR ((gene* OR mutation) AND ('diagnosis'/exp OR 'diagnosis')) |
| Comparator | N/A |
| Outcomes | N/A |
| Limits | 1993 – May 2011 |

## Selection criteria for evidence

Table 6 and Table 9 provide the PICO to be addressed by the research questions and also outlines the selection criteria that will be applied to the articles identified by the literature search. Studies that do not address the PICO, as described, will be excluded. In instances where direct evidence is lacking or is insufficient to answer the research questions, the literature search will be re-conducted according to the search terms given in Table 18 and the PICO applied to the results of that search according to the criteria outlined in Table 14 and Table 15.

All literature must also meet the following criteria:

- Fall within the search period from 1993 – May 2011;

- Non-English language articles will be excluded unless they appear to provide a higher level of evidence than the English language articles identified;

- Conducted on human subjects;

- Provide data or patients that are not duplicated in other articles. Where this occurs, only the most recent and/or comprehensive information will be selected;

- Provide data that can be extracted (ie not described graphically); and

- Have study designs that are relevant to the aspect being assessed – namely,

  o Safety: All of the relevant study designs are given in the Intervention column of Table 12. If large numbers of case series are identified, all will be reviewed but only those that are large case series and/or with long-term follow-up will have data extracted.

  o Effectiveness:

- *Direct evidence* – All of the relevant study designs are listed in the Intervention column of Table 12. However, post-test case series will be excluded. If large numbers of pre-test/post-test case series are identified, all will be identified and reviewed but only those that are large case series and/or with long-term follow-up will have data extracted.

- *Linked evidence* –

  - Predictive accuracy: All of the relevant study designs are listed in the Diagnostic accuracy column of Table 12.

  - Change in management (impact on clinical decision-making): All of the relevant study designs are listed in the Intervention column of Table 12. However, post-test case series will be excluded. If large numbers of pre-test/post-test case series are identified, all will be identified and reviewed but only those that are large case series and/or with long-term follow-up will have data extracted.

Initial eligibility on the basis of the collated study citations will be *conservatively* determined by two reviewers (ie if unclear from the abstract, or if the reviewer is unsure, the full text paper will be ordered anyway). One reviewer will then assess each of the retrieved full text articles for eligibility, with another assessing those over which there is doubt. When consensus cannot be reached, a third reviewer will independently assess the paper in question and the majority decision will prevail. A PRISMA flowchart will be used to describe the selection process for all the included studies (Liberati et al. 2009). A list of studies which met the inclusion criteria but were subsequently excluded from the review will be appended to the final report.

## Critical appraisal of individual eligible studies

Evidence retrieved from the above searches will be assessed according to the NHMRC Dimensions of Evidence which are listed in Table 11.

There are three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified for a particular intervention. The last two require expert clinical input as part of their determination. Study quality will be evaluated and reported using an appropriate instrument for quality assessment, eg quality checklists published by the NHS Centre for Reviews and Dissemination (Khan 2001), National Health and Medical Research Council (NHMRC 2000), Downs and Black (Downs & Black 1998), the QUADAS instrument from Whiting et al (2003) and the PRISMA instrument for systematic reviews (Liberati et al. 2009).

Table 11        NHMRC Dimensions of evidence

| Type of evidence | Definition |
|---|---|
| Strength of the evidence | |
|     Level | The study design used, as an indicator of the degree to which bias has been eliminated by design.* |
|     Quality | The methods used by investigators to minimise bias within a study design. |
|     Statistical precision | The $p$-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect. |
| Size of effect | The distance of the study estimate from the "null" value and the inclusion of only clinically important effects in the confidence interval. |
| Relevance of evidence | The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used. |

*See Table 12

**Table 12        Designations of levels of evidence* according to type of research question (Merlin T, Weston A & Tooher R 2009; NHMRC 2009)**

| Level | Intervention [1] | Diagnostic accuracy [2] | Prognosis | Aetiology [3] | Screening Intervention |
|---|---|---|---|---|---|
| I [4] | A systematic review of level II studies | A systematic review of level II studies | A systematic review of level II studies | A systematic review of level II studies | A systematic review of level II studies |
| II | A randomised controlled trial | A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among consecutive persons with a defined clinical presentation[6] | A prospective cohort study[7] | A prospective cohort study | A randomised controlled trial |
| III-1 | A pseudorandomised controlled trial (i.e. alternate allocation or some other method) | A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among non-consecutive persons with a defined clinical presentation[6] | All or none[8] | All or none[8] | A pseudorandomised controlled trial (i.e. alternate allocation or some other method) |
| III-2 | A comparative study with concurrent controls: Non-randomised, experimental trial[9] ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group | A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence | Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial | A retrospective cohort study | A comparative study with concurrent controls: ▪ Non-randomised, experimental trial ▪ Cohort study ▪ Case-control study |
| III-3 | A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study[10] ▪ Interrupted time series without a parallel control group | Diagnostic case-control study[6] | A retrospective cohort study | A case-control study | A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study |
| IV | Case series with either post-test or pre-test/post-test outcomes | Study of diagnostic yield (no reference standard)[11] | Case series, or cohort study of persons at different stages of disease | A cross-sectional study or case series | Case series |

[1] Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b*)* and in the accompanying Glossary.

[2] These levels of evidence apply only to studies of assessing the <u>accuracy</u> of diagnostic or screening tests. To assess the overall <u>effectiveness</u> of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes (Medical Services Advisory Committee 2005, Sackett and Haynes 2002). The evidence hierarchy given in the 'Intervention' column should be used when assessing the impact of a diagnostic test on health outcomes relative to an existing method of diagnosis/comparator test(s). The evidence hierarchy given in the 'Screening' column should be used when assessing the impact of a screening test on health outcomes relative to no screening or opportunistic screening.

[3] If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (eg. Cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilised.

[4] A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review *quality* should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.

[5] The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study (Whiting et al 2003).

[6] Well-designed population based case-control studies (eg. Population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias or spectrum effect because the spectrum of study participants will not be representative of patients seen in practice (Mulherin and Miller 2002).

[7] At study inception the cohort is either non-diseased or all at the same stage of the disease. A randomised controlled trial with persons either non-diseased or at the same stage of the disease in *both* arms of the trial would also meet the criterion for this level of evidence.

[8] All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

[9] This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (ie. Utilise A vs B and B vs C, to determine A vs C with statistical adjustment for B).

[10] Comparing single arm studies ie. Case series from two studies. This would also include unadjusted indirect comparisons (ie. Utilise A vs B and B vs C, to determine A vs C but where there is no statistical adjustment for B).

[11] Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

**Note A:** Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms (and other outcomes) are rare and cannot feasibly be captured within randomised controlled trials, in which case lower levels of evidence may be the only type of evidence that is practically achievable; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

**Note B:** When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question eg. Level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.

**Note C:** Each individual study that is attributed a "level of evidence" should be rigorously appraised using validated or commonly used checklists or appraisal tools to ensure that factors other than study design have not affected the validity of the results.

**Source:** Hierarchies adapted and modified from: NHMRC 1999; Bandolier 1999; Lijmer et al. 1999; Phillips et al. 2001

## Data extraction and synthesis of evidence

Data will be extracted by the evaluators using a standardised data extraction form which will be designed specifically for this review, or into tables developed and standardised prior to the data extraction phase.

Evidence tables will be developed for each study – outlining the level of evidence, quality assessment, authors, publication year, location, study design, study population characteristics, type of intervention, inclusion/exclusion criteria, outcomes assessed and follow-up period.

Descriptive statistics will be extracted or calculated for all safety and effectiveness outcomes in the individual studies – including numerator and denominator information, means and standard deviations, medians and inter-quartile ranges.

Relative risk/rate ratio (RR), absolute risk differences, number needed to diagnose or screen and associated 95% confidence intervals will be calculated from individual comparative studies containing count data. Mean differences and 95% confidence intervals will be extracted or calculated for normally distributed continuous outcomes in individual studies using the independent t-test. In the analysis of predictive accuracy, calculations of sensitivity, specificity, negative and positive predictive values of tests, likelihood ratios and diagnostic odds ratios, as well as 95% confidence intervals, will be undertaken where possible.

Meta-analyses of randomised controlled trials will be conducted, where appropriate, and tested for heterogeneity and publication bias. Sensitivity analyses (particularly analysing the impact of study quality) and stratification on known confounders will occur where necessary. Meta-analyses and all statistical calculations and testing will be undertaken using the biostatistical computer package, Stata version 11 (Stata Corporation 2010).

Where meta-analysis cannot or should not be conducted, a narrative meta-synthesis of the data will be undertaken.

## Assessment of the body of evidence

In addition to the individual studies, the overall body of evidence will be assessed. An evidence level from A (excellent) to D (poor) will be assigned considering each of the components outlined in the body of evidence matrix outlined in Table 13.

Table 13    Body of evidence assessment matrix (adapted from NHMRC FORM framework; (Hillier et al. 2011)

| Component | A | B | C | D |
|---|---|---|---|---|
| | Excellent | Good | Satisfactory | Poor |
| Evidence base[1] | one or more level I studies with a low risk of bias or several level II studies with a low risk of bias | one or two level II studies with a low risk of bias or a SR/several level III studies with a low risk of bias | one or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias | level IV studies, or level I to III studies/SRs with a high risk of bias |
| Consistency[2] | all studies consistent | most studies consistent and inconsistency may be explained | some inconsistency reflecting genuine uncertainty around clinical question | evidence is inconsistent |
| Clinical impact | very large | substantial | moderate | slight or restricted |
| Generalisability | population/s studied in body of evidence are the same as the target population | population/s studied in the body of evidence are similar to the target population | population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population[3] | population/s studied in body of evidence differ to target population and hard to judge whether it is sensible to generalise to target population |
| Applicability | directly applicable to Australian healthcare context | applicable to Australian healthcare context with few caveats | probably applicable to Australian healthcare context with some caveats | not applicable to Australian healthcare context |

SR = systematic review; several = more than two studies
Level of evidence determined from the NHMRC evidence hierarchy – Table 12
[2] If there is only one study, rank this component as 'not applicable'.
[3] For example, results in adults that are clinically sensible to apply to children OR psychosocial outcomes for one cancer that may be applicable to patients with another cancer

## Decision-analytic modelling methodology

A decision analytic model is a means of summarising the comparison/s that the assessment report will investigate and present. It is used to identify the extent of substitution of current technologies by the proposed technology in a specific patient group (whereas this patient group may relate to one region of a management algorithm). The decision analytic will also show how various outcomes and utilisation of health care resources are related and how they are integrated into the economic evaluation. The final model will include specification of

all relevant variables and transition probabilities to permit estimation of costs and outcomes associated with the proposed intervention and the comparator.

There will be two decision analytic models included in the economic evaluation, one for the genetic test as a means of diagnosis of VHL, and the other one for the genetic test as a means of prediction of VHL syndrome. Both models will take a societal perspective, which means any additional resources incurred that are associated with genetic test relative to currently used clinical assessment will be estimated, regardless who pays for it. Both models will take a life-time horizon. The average age of patients with symptoms will be assumed to be 26 years (Lonser et al 2003) unless Australian data is located during the assessment. The average age of family members entering the model will be determined after consulting clinical experts. A discount rate of 5% will be applied to both cost and outcomes. Extensive sensitivity analyses will be conducted to explore the robustness of the results of economic evaluation.

For patients with symptoms suggestive of VHL syndrome, genetic testing will more accurately capture the patients with VHL syndrome, compared with clinical testing alone. Although the treatment of presenting neoplasms remains the same regardless of the diagnosis, the identification of patients with a VHL mutation will offer an opportunity for more accurately targeted lifelong surveillance, which may mean that fewer patients will miss the necessary screening program due to a lower false negative rate of the proposed testing compared with clinical testing alone. The screening program enables early detection and treatment of new neoplasms that develop. As mentioned earlier, early detection and treatment is likely to result in better health outcomes, but the evidence is probably lacking. In addition, accurate diagnosis of VHL syndrome from genetic testing will save the cost of unnecessary screening due to likely comparatively lower false positive rate.

VHL genetic testing will triage family members of patients with VHL syndrome and/or VHL mutation to lifelong screening. Therefore, the family members who do not show symptoms of VHL syndrome and have not inherited the genetic mutation will be excluded from the lifelong screening, which may be cost saving to Australian society – the adverse events, if any, associated with lifelong screening will also be avoided among these people; whilst, family members with the mutation will receive targeted screening resulting in early detection and treatment and potentially better health outcomes.

## Appendix A

### Selection criteria for linked evidence

In the absence of direct evidence, a linked evidence approach will be attempted, where evidence of predictive accuracy, and change in clinical management are linked to provide an assessment of the effectiveness of using genetic testing in the diagnosis of VHL syndrome. Evidence of treatment effectiveness will not be assessed, as it is expected that patients presenting with VHL-associated neoplasms would be treated the same, regardless of the method of diagnosis. It is expected that family members without a pathogenic mutation would avoid the need for screening, resulting in a change in a management. However, these family members are unlikely to have any change in treatment, or therefore health outcomes based on the avoidance of screening. The effectiveness (health impact) of this change in management in family members will therefore also not be assessed in the systematic review. The inclusion criteria for a linked assessment are outlined in Table 14 to Table 17.

The clinical diagnosis of VHL syndrome is defined as:

- Family history of VHL, and a haemangioblastoma (retinal or CNS), phaeochromocytoma, or clear cell renal carcinoma; or

- 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).

Table 14    Inclusion criteria for identification of studies relevant to assessment of the predictive accuracy of genetic testing for VHL syndrome (index patient)

| Characteristic | Criteria |
|---|---|
| Study design | All study designs in the Diagnostic Accuracy column of Table 12 will be included. |
| Population | Patients presenting with one or more clinical features suggestive of VHL syndrome |
| Intervention/test | VHL genetic testing to diagnose *VHL* gene mutations and clinical diagnosis from family history, clinical history, tests including CT, MRI, ultrasound, hearing test, eye exam, blood tests, other tests as appropriate to identify any signs of disease other than presenting complaint |
| Comparator | Clinical diagnosis from family history, clinical history, tests including CT, MRI, ultrasound, hearing test, eye exam, blood tests, other tests as appropriate to identify any signs of disease other than presenting complaint |
| Reference standard | Clinical diagnosis determined from long term follow-up |
| Outcome | Predictive accuracy outcomes: Sensitivity and specificity (and therefore rates of false positives and negatives), positive and negative likelihood ratios, positive and negative predictive values (and therefore false alarm and reassurance rates), diagnostic odds ratios, receiver operator characteristic curves, area under the curve, accuracy |
| Search period | 1993 – May 2011 |
| Language | Non-English language articles will be excluded unless they provide a higher level of evidence than the English language articles identified |

**Table 15    Inclusion criteria for identification of studies relevant to assessment of a change in patient management as a result of genetic testing for VHL syndrome (index patient)**

| Characteristic | Criteria |
|---|---|
| Study design | All study designs in the Intervention column of Table 12, with the exception of post-test case series, will be included. If large numbers of pre-test/post-test case series are identified, all will be identified and reviewed but only those that are large case series and/or with long-term follow-up will have data extracted. |
| Population | Patients presenting with one or more clinical features suggestive of VHL syndrome |
| Intervention/test | VHL genetic testing to diagnose *VHL* gene mutations and clinical diagnosis from family history, clinical history, tests including CT, MRI, ultrasound, hearing test, eye exam, blood tests, other tests as appropriate to identify any signs of disease other than presenting complaint |
| Comparator | Clinical diagnosis from family history, clinical history, tests including CT, MRI, ultrasound, hearing test, eye exam, blood tests, other tests as appropriate to identify any signs of disease other than presenting complaint |
| Outcome | Rate and type of referral, frequency and compliance with clinical screening, rate and type of treatment, type of referral, hospital separations and re-admissions, hospital length of stay |
| Search period | 1993 – May 2011 |
| Language | Non-English language articles will be excluded unless they provide a higher level of evidence than the English language articles identified |

**Table 16    Inclusion criteria for identification of studies relevant to assessment of the predictive accuracy of genetic testing for VHL syndrome (family members)**

| Characteristic | Criteria |
|---|---|
| Study design | All study designs in the Diagnostic Accuracy column of Table 12 will be included. |
| Population | Relatives of patients with a diagnosed VHL mutation |
| Intervention/test | Genetic testing for clinically relevant mutations in the *VHL* gene ± clinical testing (CT, MRI, ultrasound, hearing test, eye exam, and blood tests) and routine lifelong screening for neoplasms using CT, MRI, ultrasound, hearing test, eye exam, and blood tests |
| Comparator | Clinical testing (CT, MRI, ultrasound, hearing test, eye exam, and blood tests) and routine lifelong screening for neoplasms using CT, MRI, ultrasound, hearing test, eye exam, and blood tests |
| Reference standard | Clinical diagnosis determined from life-long follow-up |
| Outcome | Predictive accuracy outcomes: Sensitivity and specificity (and therefore rates of false positives and negatives), positive and negative likelihood ratios, positive and negative predictive values, diagnostic odds ratios, receiver operator characteristic curves, area under the curve, accuracy |
| Search period | 1993 – May 2011 |
| Language | Non-English language articles will be excluded unless they provide a higher level of evidence than the English language articles identified |

Table 17    Inclusion criteria for identification of studies relevant to assessment of a change in patient management as a result of genetic testing for VHL syndrome (family members)

| Characteristic | Criteria |
|---|---|
| Study design | All study designs in the Intervention column of Table 12, with the exception of post-test case series, will be included. If large numbers of pre-test/post-test case series are identified, all will be identified and reviewed but only those that are large case series and/or with long-term follow-up will have data extracted. |
| Population | Relatives of patients with a diagnosed VHL mutation |
| Intervention/test | Genetic testing for clinically relevant mutations in the *VHL* gene ± clinical testing (CT, MRI, ultrasound, hearing test, eye exam, and blood tests) and routine lifelong screening for neoplasms using CT, MRI, ultrasound, hearing test, eye exam, and blood tests |
| Comparator | Clinical testing (CT, MRI, ultrasound, hearing test, eye exam, and blood tests) and routine lifelong screening for neoplasms using CT, MRI, ultrasound, hearing test, eye exam, and blood tests |
| Outcome | Frequency and compliance with clinical screening, rates of treatment, method of treatment, rates of referral, type of referral, hospital separations and re-admissions, hospital length of stay |
| Search period | 1993 – May 2011 |
| Language | Non-English language articles will be excluded unless they provide a higher level of evidence than the English language articles identified |

## Search terms for a linked evidence approach (if required)

Table 18    Suggested search terms for VHL genetic testing (linked evidence)

| Element of clinical question | Suggested search terms |
|---|---|
| Test accuracy | 'von hippel lindau disease'/exp OR 'von hippel lindau' OR 'vhl gene' OR 'vhl mutation' OR 'vhl' AND [1993-2011]/py<br>AND<br>'diagnosis, measurement and analysis'/exp OR 'sensitivity and specificity'/exp OR 'sensitivity' OR 'specificity' OR 'accuracy' OR 'diagnostic error'/exp OR 'false negative' OR 'false positive' OR 'predictive value' OR 'likelihood ratio' |
| Change in management of patients identified with VHL mutation | 'von hippel lindau disease'/exp OR 'von hippel lindau' OR 'vhl gene' OR 'vhl mutation' OR 'vhl' AND [1993-2011]/py<br>AND<br>'therapy'/exp OR 'therapy' OR 'disease management'/exp OR 'management' OR 'patient care' OR 'treatment' OR 'therapy' OR 'surveillance' OR 'monitoring' OR 'screening' |

## Appendix B

### Health Technology Assessment Agency Websites

**AUSTRALIA**

| | |
|---|---|
| Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) | http://www.surgeons.org/Content/NavigationMenu/Research/ASERNIPS/default.htm |
| Centre for Clinical Effectiveness | http://www.southernhealth.org.au/cce |
| Centre for Health Economics, Monash University | http://www.buseco.monash.edu.au/centres/che/ |

**AUSTRIA**

| | |
|---|---|
| Institute of Technology Assessment / HTA unit | http://www.oeaw.ac.at/ita |

**CANADA**

| | |
|---|---|
| Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) | http://www.aetmis.gouv.qc.ca/site/home.phtml |
| Alberta Heritage Foundation for Medical Research (AHFMR) | http://www.ahfmr.ab.ca/publications.html |
| Alberta Institute of Health Economics | http://www.ihe.ca/ |
| The Canadian Agency for Drugs And Technologies in Health (CADTH) | http://www.cadth.ca/index.php/en/ |
| Canadian Health Economics Research Association (CHERA/ACRES) – Cabot database | http://www.mycabot.ca |
| Centre for Health Economics and Policy Analysis (CHEPA), McMaster University | http://www.chepa.org |
| Centre for Health Services and Policy Research (CHSPR), University of British Columbia | http://www.chspr.ubc.ca |
| Health Utilities Index (HUI) | http://www.fhs.mcmaster.ca/hug/index.htm |
| Institute for Clinical and Evaluative Studies (ICES) | http://www.ices.on.ca |
| Saskatchewan Health Quality Council (Canada) | http://www.hqc.sk.ca |

**DENMARK**

| | |
|---|---|
| Danish Centre for Evaluation and Health Technology Assessment (DACEHTA) | http://www.sst.dk/english/dacehta.aspx?sc_lang=en |
| Danish Institute for Health Services Research (DSI) | http://dsi.dk/english/ |

**FINLAND**

| | |
|---|---|
| Finnish Office for Health Technology Assessment (FINOHTA) | http://finohta.stakes.fi/EN/index.htm |

**FRANCE**

| | |
|---|---|
| The Haute Autorité de santé (HAS) - or French National Authority for Health | http://www.has-sante.fr/portail/jcms/c_5443/english?cid=c_5443 |

**GERMANY**

| | |
|---|---|
| German Institute for Medical Documentation and Information (DIMDI) / HTA | http://www.dimdi.de/static/en/index.html |
| Institute for Quality and Efficiency in Health Care (IQWiG) | http://www.iqwig.de |

**THE NETHERLANDS**

| | |
|---|---|
| Health Council of the Netherlands Gezondheidsraad | http://www.gezondheidsraad.nl/en/ |
| Institute for Medical Technology Assessment (Netherlands) | http://www.imta.nl/ |

**NEW ZEALAND**

New Zealand Health Technology Assessment (NZHTA)    http://nzhta.chmeds.ac.nz/

**NORWAY**

Norwegian Knowledge Centre for the Health Services    http://www.kunnskapssenteret.no

**SPAIN**

Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III"I/Health Technology Assessment Agency (AETS)    http://www.isciii.es/

Andalusian Agency for Health Technology Assessment (Spain)    http://www.juntadeandalucia.es/

Catalan Agency for Health Technology Assessment  (CAHTA)    http://www.gencat.cat

**SWEDEN**

Center for Medical Health Technology Assessment    http://www.cmt.liu.se/?l=en&sc=true

Swedish Council on Technology Assessment in Health Care (SBU)    http://www.sbu.se/en/

**SWITZERLAND**

Swiss Network on Health Technology Assessment (SNHTA)    http://www.snhta.ch/

**UNITED KINGDOM**

National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA)    http://www.hta.ac.uk/

NHS Quality Improvement Scotland    http://www.nhshealthquality.org/

National Institute for Clinical Excellence (NICE)    http://www.nice.org.uk/

The European Information Network on New and Changing Health Technologies    http://www.euroscan.bham.ac.uk/

University of York NHS Centre for Reviews and Dissemination (NHS CRD)    http://www.york.ac.uk/inst/crd/

**UNITED STATES**

Agency for Healthcare Research and Quality  (AHRQ)    http://www.ahrq.gov/clinic/techix.htm

Harvard School of Public Health    http://www.hsph.harvard.edu/

Institute for Clinical and Economic Review (ICER)    http://www.icer-review.org/

Institute for Clinical Systems Improvement (ICSI)    http://www.icsi.org

Minnesota Department of Health (US)    http://www.health.state.mn.us/htac/index.htm

National Information Centre of Health Services Research and Health Care Technology (US)    http://www.nlm.nih.gov/hsrph.html

Oregon Health Resources Commission (US)    http://egov.oregon.gov/DAS/OHPPR/HRC/about_us.shtml

Office of Health Technology Assessment Archive (US)    http://fas.org/ota

U.S. Blue Cross/ Blue Shield Association Technology Evaluation Center (Tec)    http://www.bcbs.com/blueresources/tec/

Veteran's Affairs Research and Development Technology Assessment Program (US)    http://www.research.va.gov/default.cfm

## Appendix C

Literature Sources

Electronic bibliographic databases will be searched to find relevant studies (those meeting the inclusion criteria) addressing each of the research questions developed for this MSAC assessment. These databases are described in Table 19. The VHL gene has only been described in the literature after 1993, therefore the search period will be restricted from 1993 (or if inception of the database is later, from that date) until May 2011.

Table 19    Bibliographic databases

| Electronic database | Time period |
|---|---|
| Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database | 1993 – May 2011 |
| Web of Science – Science Citation Index Expanded | 1993 – May 2011 |
| Current Contents | 1998 – May 2011 |
| Embase.com (including Embase and Medline) | 1993 – May 2011 |
| PubMed | 1993 – May 2011 |
| CINAHL | 1993 – May 2011 |
| EconLit | 1993 – May 2011 |
| PsycINFO (for ethical issues only) | 1993 – May 2011 |

Additional sources of literature – peer-reviewed or grey literature – will be sought from the sources outlined in Table 20, and from the health technology assessment agency websites provided in Appendix B. Websites of specialty organisations will also be searched for any potentially relevant information.

Table 20    Additional sources of literature

| Source | Location |
|---|---|
| *Internet* | |
| NHMRC- National Health and Medical Research Council (Australia) | http://www.health.gov.au/nhmrc/ |
| US Department of Health and Human Services (reports and publications) | http://www.os.dhhs.gov/ |
| New York Academy of Medicine Grey Literature Report | http://www.nyam.org/library/greylit/index.shtml |
| Trip database | http://www.tripdatabase.com |
| Current Controlled Trials metaRegister | http://controlled-trials.com/ |
| National Library of Medicine Health Services/Technology Assessment Text | http://text.nlm.nih.gov/ |
| U.K. National Research Register | http://www.update-software.com/National/ |
| Google Scholar | http://scholar.google.com/ |
| *Hand Searching  (Journals from 2010-2011)* | |
| | Library or electronic access |
| *Expert Clinicians* | Library or electronic access |
| Studies other than those found in regular searches | MSAC Expert Standing Panel (MESP) |
| *Pearling* | |
| All included articles will have their reference lists searched for additional relevant source material | |

## Specialty websites

| | |
|---|---|
| VHL Family Alliance | http://www.vhl.org/ |
| The VHL mutations database | http://www.umd.be/VHL/ |
| GeneTests<br>Laboratories offering clinical testing for VHL syndrome | http://www.ncbi.nlm.nih.gov/sites/GeneTests/?db=GeneTests<br>http://www.ncbi.nlm.nih.gov/sites/GeneTests/lab/clinical_disease_id/2171?db=genetests |
| The Royal College of Pathologists of Australasia Catalogue of Genetic Tests and Laboratories | http://genetictesting.rcpa.edu.au/ |
| Genetics Home Reference<br>Von Hippel-Lindau syndrome | http://ghr.nlm.nih.gov/condition/von-hippel-lindau-syndrome |
| Cancer.Net<br>Von Hippel-Lindau Syndrome | http://www.cancer.net/patient/Cancer+Types/Von+Hippel-Lindau+Syndrome |
| eMedicine - von Hippel-Lindau Disease | http://emedicine.medscape.com/article/950063-overview |
| Cancer Council Australia<br>Types of family cancer | http://www.cancer.org.au//aboutcancer/familycancers/typesfamilycancer.htm |

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