Australian Government

Department of Health

MSAC Application 1702

Abdominal Magnetic Resonance Imaging (MRI) for rare genetic conditions associated with increased risk of renal tumours

Ratified
PICO Confirmation

Summary of PICO/PPICO criteria to define questions to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC).

Table 1 PICO for Abdominal MRI for detection of new tumours in rare genetic conditions associated with increased risk of renal tumours: PICO Set 1

Component	Description
Population	Patients with rare heritable genetic conditions that are strongly associated with the development of renal tumours over time, who may or may not be currently undergoing stable, disease-specific therapy. These conditions currently identified are: • Tuberous Sclerosis Complex (TSC); • Von Hippel-Lindau disease (VHL); • Birt-Hogg-Dube syndrome (BHD); • Hereditary papillary renal carcinoma (Type 1 papillary); • Hereditary leiomyomatosis and renal cell cancer (HLRCC); • Cowden syndrome (*PTEN* Hamartoma Tumour Syndrome spectrum); • *BAP1*-associated cancer syndrome; • *SDH*-associated renal cancer (risk for phaeochromocytoma and paraganglioma); • Familial clear renal cell carcinoma with chromosome 3 translocation; • Microphthalmia-associated transcription factor (MiTF)-associated renal cell carcinoma (RCC); and • Hereditary non-polyposis colon cancer (HNPCC; Lynch syndrome). While these are the currently defined conditions, other rare genetic disorders associated with the increased risk of developing renal tumours are also intended to be eligible for this service.
Prior tests	Genetic testing to confirm germline pathogenic variants of the genes associated with the condition in question. However, the diagnosis may not require confirmatory genetic testing and may be a clinical diagnosis alone, where there are standardised phenotypic diagnostic criteria applicable.
Intervention	Magnetic Resonance Imaging (MRI) of the abdomen using gadolinium-based contrast (where applicable); annual surveillance.
Comparators	Computed tomography (CT) or ultrasound (US).
Reference standard	Biopsy and histopathology.
Outcomes	Safety outcomes: • Adverse reaction to contrast agent. • Cumulative effects of multiple contrast agent injections. • Claustrophobia requiring the administration of sedation or general anaesthetic.

Component	Description
	• Harms from follow-up testing. • Other adverse events arising from MRI. • Exposure to ionising radiation. Effectiveness outcomes: • Mortality. • Time to diagnosis of tumours. • Monitoring growth and number of tumours. • Time from diagnosis to treatment. • Changes to management of treatment, for example: - use of mammalian target of rapamycin inhibitor (mTORi) therapy (TSC); - impacts on emergency presentations for spontaneous angiomyolipomas (AML) bleeding (TSC); - curative management (surgical and/or systemic cytotoxic therapy) for malignant tumours. • Quality of life. Test accuracy outcomes: • Sensitivity and specificity compared to existing modalities. Economic outcomes: • Healthcare resources. • Cost-effectiveness. • Total Australian Government healthcare costs.
Assessment questions	What is the safety, effectiveness and cost-effectiveness of abdominal MRI surveillance versus computed tomography scans or ultrasound surveillance in patients with rare heritable genetic conditions that are strongly associated with the development of renal tumours?

Table 2 PICO for MRI to assess response after disease-specific therapeutic intervention in rare genetic conditions associated with increased risk of renal tumours: PICO Set 2

Component	Description
Population	Patients with rare heritable genetic conditions that are strongly associated with the development of renal tumours who require assessment of response to disease-specific therapeutic intervention. These conditions currently identified are: • Tuberous Sclerosis Complex (TSC); • Von Hippel-Lindau disease (VHL); • Birt-Hogg-Dube syndrome (BHD); • Hereditary papillary renal carcinoma (Type 1 papillary); • Hereditary leiomyomatosis and renal cell cancer (HLRCC); • Cowden syndrome-(*PTEN* Hamartoma Tumour Syndrome spectrum); • *BAP1*-associated cancer syndrome; • *SDH*-associated renal cancer (risk for phaeochromocytoma and paraganglioma); • Familial clear renal cell carcinoma with chromosome 3 translocation; • Microphthalmia-associated transcription factor (MiTF)-associated renal cell carcinoma (RCC); and • Hereditary non-polyposis colon cancer (HNPCC; Lynch syndrome). While these are the currently defined conditions, other rare genetic disorders associated with the increased risk of developing renal tumours are also intended to be eligible for this service.
Prior tests	Previous abdominal computed tomography (CT) scan, ultrasound (US), or MRI to identify benign or malignant renal tumours requiring treatment followed by biopsy/histopathology to confirm morphological diagnosis of the tumour
Intervention	Magnetic Resonance Imaging (MRI) of the abdomen using gadolinium-based contrast (where applicable) to evaluate changes in clinical condition or suspected complications of known renal tumours arising between the annual surveillance MRI, or where a disease specific line of treatment has been initiated and an assessment of patient responsiveness to this treatment is required, no more than once per patient in a three-month period.
Comparator/s	Computed tomography (CT) scans or ultrasound (US)
Reference standard	Biopsy and histopathology for morphological diagnosis, and/or CT or US.
Outcomes	Safety outcomes: • Adverse reaction to contrast agent. • Cumulative effects of multiple contrast agent injections. • Claustrophobia requiring the administration of sedation or general anaesthetic. • Harms from follow-up testing. • Other adverse events arising from MRI. • Exposure to ionising radiation.

Component	Description
	Effectiveness outcomes: • Mortality. • Time to diagnosis of tumours. • Monitoring growth, complications or recurrence of tumours. • Time from diagnosis to treatment. • Assessing tumour response to treatment. • Changes to management of treatment, for example: - use of mammalian target of rapamycin inhibitor (mTORi) therapy (TSC); - impacts on emergency presentations for spontaneous angiomyolipomas (AML) bleeding (TSC); - curative management (surgical and/or systemic cytotoxic therapy) for malignant tumours. • Quality of life. Test accuracy outcomes: • Sensitivity and specificity compared to existing modalities. Economic outcomes: • Healthcare resources. • Cost-effectiveness. • Total Australian Government healthcare costs.
Assessment questions	What is the safety, effectiveness and cost-effectiveness of abdominal MRI versus US or CT for assessing changes in clinical condition, suspected complications or response to disease-specific therapeutic intervention in patients who have developed renal tumours associated with a rare heritable genetic condition?

Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of abdominal magnetic resonance imaging (MRI) for patients with rare genetic conditions associated with increased risk of renal tumours from Rare Voices Australia was received by the Department of Health.

The application claimed that:

- MRI was a superior diagnostic test compared to existing funded imaging modalities.
- MRI was superior in terms of safety as it is associated with decreased adverse effects compared to computed tomography (CT).
- MRI was superior in terms of effectiveness as it provided an overall benefit in mortality through reduction in catastrophic bleeding from angiomyolipomas (AMLs) and improved outcomes of malignant tumours through early diagnosis.

The application requests MBS listing of MRI for (i) annual surveillance and (ii) assessment of response to treatment three to six months post initiation of treatment. As such, there are two PICO Sets, which differ with respect to (i) the patient population and (ii) the intervention ((a) surveillance versus (b) assessment of complications or changes in clinical condition or response to disease-specific therapeutic intervention). There are no differences between the PICO Sets with regard to the comparator and most outcomes (those related to one PICO Set are explicitly reported as such). To avoid unnecessary duplication, the 'Population', 'Intervention', 'Reference Standard' and 'Proposal for public funding' sections of this PICO Confirmation will be split to describe the characteristics of these with respect to the PICO Set, all other sections are relevant to both PICO Sets.

PICO criteria

Population

PICO Set 1

The population is patients with rare defined genetic conditions that are strongly associated with the development of renal tumours over time, who may or may not be currently undergoing stable, disease-specific therapy.

These conditions are currently defined as:

- Tuberous Sclerosis Complex (TSC);
- Von Hippel-Lindau disease (VHL);
- Birt-Hogg-Dube syndrome (BHD);
- Hereditary papillary renal carcinoma (Type 1 papillary);
- Hereditary leiomyomatosis and renal cell cancer (HLRCC);
- Cowden syndrome (*PTEN* Hamartoma Tumor Syndrome spectrum) ;
- *BAP1*-associated cancer syndrome;
- *SDH*-associated renal cancer (risk for phaeochromocytoma and paraganglioma); and
- Familial clear renal cell carcinoma with chromosome 3 translocation.

PASC noted that two further syndromes could be included in both PICO Sets:

- *Microphthalmia-associated transcription factor (MiTF)-associated renal cell carcinoma (RCC); and*
- *Hereditary non-polyposis colon cancer (HNPCC; Lynch syndrome - associated with an increased risk of urothelial cancers [often high-grade and with a propensity to occur in the upper urinary tract]).*
- *Additional syndromes are likely to be identified over time.*

Each of these syndromes has its own molecular alteration, and these are often reflected in distinctive histologic features and clinical course (Choueri 2022). The application notes that these inheritable conditions are together responsible for approximately 4% of all renal tumours (Lineman 2001).

While these are the currently defined conditions, other rare genetic disorders associated with the increased risk of developing renal tumours are also intended to be eligible for this service.

Table 3 presents a brief summary of key characteristics of each currently defined condition.

Table 3 Clinical and molecular characteristics of the most common hereditary kidney tumour syndromes

Syndrome	Gene (OMIM #)	Major clinical presentations	Frequency/rarity
Tuberous Sclerosis Complex (TSC)	*TSC1* (191100), *TSC2* (191092)	(Discussed below)	Incidence of 1:6,000 and prevalence of 8.8:100, 000 (O'Callaghan 1998 and Osborne 1991) .
Von Hippel- Lindau	*VHL* (193300)	(Discussed below)	Incidence of 1:36,000 and prevalence 1:91,000 in Australia (MSAC 1153 Assessment Report, p5)
Birt-Hogg-Dubé syndrome	*FLCN* (134150)	Small dome-shaped papules on the face, neck, and upper trunk (fibrofolliculomas), increased risk of renal neoplasia and spontaneous pneumothorax	1-2 per million (Muller 2021)
Hereditary papillary renal carcinoma (Type 1 papillary)	*MET* (605074)	Multifocal bilateral renal cell tumours	HPRC is considered to be rare. The number of people and families who have HPRC is unknown. However, there are approximately 30 families in published medical reports. (Cancer.Net, 2020, HPRC)
Hereditary leiomyomatosis and renal cell carcinoma	*FH* (150800)	Leiomyomas of skin and uterus, unilateral solitary and aggressive renal cell tumours, PET- positive adrenal adenomas	HLRCC is a rare condition that has been reported in approximately 300 families worldwide. Researchers suggest that it may be underdiagnosed.(Medlineplus, HLRCC)
BAP-1 tumour pre-disposition syndrome	*BAP1* (614327)	Melanoma (uveal and cutaneous) kidney cancer, mesothelioma	The prevalence of *BAP1*-TPDS is unknown. Based on data from the Genome Aggregation Database (gnomAD), the carrier frequency is 1:26,837 in the general population. (Pilarski 2016)
Hereditary paraganglioma/ pheochromocytoma syndrome	*SDHA* (614165), *SDHB* (115310), *SDHC* (605373), *SDHD* (168000)	Head and neck paraganglioma and adrenal or extra-adrenal pheochromocytomas, benign lung lesions, GIST tumours	Hereditary paraganglioma-pheochromocytoma occurs in approximately 1 in 1 million people. (Medlineplus HPPS)
Cowden syndrome	*PTEN* (158350)	Multiple hamartomas that can affect various areas of the body, breast cancer, thyroid cancer, endometrial cancer, renal cell cancer	It is estimated that CS affects about 1 in every 200,000 individuals. (Cancer.Net 2020, Cowden syndrome)

Syndrome	Gene (OMIM #)	Major clinical presentations	Frequency/rarity
Familial clear renal cell carcinoma with chromosome 3 translocation	Translocation of chromosome 3 (potentially includes any of *VHL*, *PBRM1*, *BAP1*, and *SETD2)*	Clear cell carcinoma	Very rare, described within individual families in case series.
Microphthalmia-associated transcription factor (MiTF)-associated RCC	MITF (156845)	RCC (various subtypes)	Allele frequency 0.0013; predisposition to melanoma
Hereditary non-polyposis colon cancer (HNPCC; Lynch syndrome	MSH1, MSH2, MSH6, PMS2, EPCAM	Urothelial cancer (6%) - aggressive	Estimated carrier frequency 1:280

Source: adapted from NCCN guidelines version 1.2021 Hereditary renal cell carcinomas; OMIM: On-line Mendelian Inheritance in Man (www.omim.org).
GIST = gastro-intestinal stromal tumour; HLRCC = Hereditary leiomyomatosis and renal cell carcinoma; HPPS = Hereditary paraganglioma/pheochromocytoma syndrome; HPRC = hereditary papillary renal carcinoma; TPDS = Tumour predisposition syndrome

Tuberous Sclerosis Complex (TSC)

Tuberous Sclerosis Complex (TSC) is a genetic disease caused by mutations in the tumour suppressor genes *TSC1* and *TSC2*, located on chromosomes 9 and 16 (van Slegtenhorst 1997 and Consortium ECTS 1993, cited in Amin 2019). The protein products of TSC1 and *TSC2* (hamartin and tuberin) function together within the cell and have an inhibitory effect on the mammalian target of rapamycin (mTOR), a protein kinase that influences cell growth and division and the synthesis of proteins and other cell components (Tee 2002 referenced in Amin 2019). Mutations in either *TSC1* or *TSC2* lead to over-activation of the mTOR pathway and relatively uncontrolled cell growth that causes growth of benign tumours (hamartomas) in various organs, such as the brain, kidneys, skin, heart, lungs and bones (Kwiatkowski 2003 cited in Amin 2019).

The application states that TSC has an incidence of 1:6000 and prevalence of 8.8:100000 (O'Callaghan 1998 and Osborne 1991). The incidence was estimated in a UK study to be 1 per 5800 live births. Approximately two-thirds of cases occur sporadically (Osborne 1991 cited in Northrup 2021). A more recent study in Germany estimated the incidence rate to be from 1:6760 to 1:13520 live births (Ebrahimi-Fakhari 2018 cited in Northrup 2021). Of the requested population, the majority of treated patients would be patients with TSC.

The management of TSC has varied depending on treating physician, local and national policies and funding. The International TSC Clinical Consensus Group reaffirmed the importance of independent genetic diagnostic criteria and clinical diagnostic criteria. Identification of a pathogenic variant in *TSC1* or *TSC2* is sufficient for the diagnosis or prediction of TSC regardless of clinical findings (Northrup 2021). Determination of pathogenicity of genetic variants of *TSC1* or *TSC2* should follow standards and guidelines of the American College of Medical Genetics (ACMG) for interpretation of sequence variants. Between 10% and 15% of patients with TSC meeting clinical diagnostic criteria have no mutation identified by conventional genetic testing. Therefore, failure to identify a pathogenic variant in *TSC1* or *TSC2* does not exclude a diagnosis of TSC (Norhtrup 2021). Consequently, TSC may be diagnosed based on clinical features alone. Table 4 presents the clinical features for diagnosis of TSC.

Table 4 Clinical features of TSC

Major Criteria	Minor Criteria
• Hypomelanotic macules (≥3; at least 5 mm diameter) • Angiofibroma (≥3) or fibrous cephalic plaque Ungual fibromas (≥2) • Shagreen patch • Multiple retinal hamartomas • Subependymal nodule (≥2) • Subependymal giant cell astrocytoma • Cardiac rhabdomyoma • LAM* • Angiomyolipomas (≥2)*	• "Confetti" skin lesions • Dental enamel pits (≥3) • Intraoral fibromas (≥2) • Retinal achromic patch • Nonrenal hamartomas • Sclerotic bone lesions

Source: Table 2, p53 of Northrup (2021)
Abbreviations: LAM . Lymphangiomyomatosis TSC . Tuberous sclerosis complex
Definite TSC: 2 major features or 1 major feature with 2 minor features.
Possible TSC: either 1 major feature or 2 minor features.
Genetic diagnosis: A pathogenic variant in *TSC1* or *TSC2* is diagnostic for TSC (most TSC-causing variants are sequence variants that clearly prevent *TSC1* or *TSC2* protein production. Some variants compatible with protein production [e.g., some missense changes] are well established as disease-causing; other variant types should be considered with caution).
* A combination of the 2 major clinical features LAM and angiomyolipomas without other features does not meet criteria for a definite diagnosis.

As shown in Table 4, patients with TSC experience a range of symptoms across various organ systems. The key organs impacted include the brain, skin, kidneys, lungs, heart and eyes, resulting in clinical manifestations including seizures, neuropsychiatric conditions, spontaneous haemorrhage from the kidneys, cardiac arrhythmias and lung disease.

Up to 80% of patients with TSC experience angiomyolipoma (AML). Patients are predominantly young (mean age of 18 years), and the AML has a tendency for rapid growth, larger lesions, and may be both bilateral and multiple in their presentation, without a sex difference in incidence (Lee 2019, Kingswood 2016 cited in Restrepo 2022).

The application states that 21-40% of all people with TSC experience bleeding from AMLs or chronic kidney disease. The application notes that it has been demonstrated that treatment of patients with large AMLs at increased risk of bleeding with the mTOR inhibitor everolimus is effective at reducing the size of AMLs and preventing bleeding complications. Everolimus is available on the Pharmaceutical Benefits Scheme (PBS) in Australia for the treatment of visceral tumours associated with TSC.

In addition to the increased risk for retroperitoneal haemorrhage, complications of TSC-associated renal AML are chronic arterial hypertension and chronic kidney disease (CKD), the latter with a fivefold higher rate and a 30-year earlier onset (CKD stage 3) compared to the general population (Flum 2016, Samuels 2017, Kingswood 2016, cited in Restrepo 2022).

The updated international tuberous sclerosis complex diagnostic criteria and surveillance and management recommendations (Northrup 2021) indicate a wide variety of surveillance and management recommendations across many organ areas, this is presented in Table 5.

Table 5 International surveillance and management recommendations for newly diagnosed or suspected TSC

Organ system or specialty area	Recommendations
Genetics	• Obtain three-generation family history to assess for additional family members at risk of TSC. • Offer genetic testing for family counselling or when TSC diagnosis is in question but cannot be clinically confirmed.
Brain	• Obtain MRI of the brain to assess for the presence of tubers, SEN, migrational defects, and SEGA. • During infancy, educate parents to recognize infantile spasms and focal seizures, even if none have occurred at the time of first diagnosis • Obtain MRI of the brain to assess for the presence of tubers, SEN, migrational defects, and SEGA. • During infancy, educate parents to recognize infantile spasms and focal seizures, even if none have occurred at the time of first diagnosis
TAND	• Perform comprehensive assessment for all levels of potential TAND manifestations • Refer as appropriate to suitable professionals to initiate evidence-based interventions based on the TAND profile of above-identified needs. • Provide parent/caregiver education and training about TAND to ensure families know what to look out for in emerging TAND manifestations (e.g. autism spectrum disorder, language disorders, attention-deficit/hyperactivity disorder, anxiety disorders). • Provide psychological and social support to families around diagnosis, coming to terms with the diagnosis of TSC and TAND, and ensure strategies are in place to support caregiver well-being.
Kidney	• Obtain MRI of the abdomen to assess for the presence of angiomyolipomas and renal cysts. • Screen for hypertension by obtaining an accurate blood pressure. • Evaluate renal function by determination of GFR.
Lung	• Inquire about tobacco exposure, connective tissue disease manifestations, signs of chyle leak, and pulmonary manifestations of dyspnea, cough, and spontaneous pneumothorax in all adult patients with TSC. • Perform baseline chest CT in all females, and symptomatic males, starting at age 18 years or older. • Perform baseline PFTs and 6MWT in patients with evidence of cystic lung disease consistent with LAM on the screening chest CT.
Skin	• Perform a detailed clinical dermatologic inspection/examination.
Teeth	• Perform a detailed clinical dental inspection/examination
Heart	• Consider fetal echocardiography to detect individuals with high risk of heart failure after delivery when rhabdomyomas are identified via prenatal ultrasound. • Obtain an echocardiography in paediatric patients, especially if younger than age three years. • Obtain an electrocardiography at all ages to assess for underlying conduction defects.
Eye	• Perform a complete ophthalmologic evaluation, including dilated fundoscopy, to assess for retinal findings (astrocytic hamartoma and achromic patch) and visual field deficits.

Source: Table 3, p53 of Northrup 2021.

6MWT = 6-Minute walk test; CT = Computed tomography; EEG = Electroencephalography; GFR = Glomerular filtration rate; LAM = Lymphangiomyomatosis; MRI = Magnetic resonance imaging; PFT = Pulmonary function test; SEGA = Subependymal gain cell astrocytoma; SEN = Subependymal nodules; TAND = TSC-associated neuropsychiatric disorder; TSC = Tuberous sclerosis complex

Table 6 presents the international kidney-related surveillance and management recommendations for patients already diagnosed with definite or possible TSC.

Table 6 International Surveillance and Management Recommendations for Patients Already Diagnosed with Definite or Possible TSC

Organ system[a]	Recommendations
Kidney	• Obtain MRI of the abdomen to assess for the progression of angiomyolipoma and renal cystic disease every 1-3 years throughout the lifetime of the patient. • Assess renal function including determination of glomerular filtration rate, proteinuria, and blood pressure at least annually. • Embolisation followed by corticosteroids is the first-line therapy for angiomyolipoma presenting with acute haemorrhage. • Nephrectomy is to be avoided. For asymptomatic, growing angiomyolipoma measuring larger than 3 cm in diameter, treatment with an mTOR is the recommended first-line therapy. Selective embolisation or kidney-sparing resection are acceptable second-line treatments for asymptomatic angiomyolipoma.

Source: Table 4, p56 of Northrup (2021).
cm = centimetre; MRI = magnetic resonance imaging; mTOR = mechanistic target of rapamycin; TSC = Tuberous sclerosis complex
[a] Northrup (2021) included recommendations across several organ systems. For concision, only the kidney-related recommendations are presented.

Northrup (2021) indicates that for patients presenting with AML with acute haemorrhage, embolisation followed by corticosteroids is the first line therapy, and notes that nephrectomy is to be avoided.

Northrup (2021) also notes that for asymptomatic, growing AML measuring larger than 3 centimetres (cm) in diameter, treatment with a mammalian target of rapamycin inhibitor (mTORi; e.g., everolimus or sirolimus) is the recommended first-line therapy, and that selective embolisation or kidney-sparing resection are acceptable second-line treatments for asymptomatic angiomyolipoma.

It should be noted that the PBS criteria for reimbursement of everolimus in TSC patients (Items 2818H and 11258M) states that a 'patient must not be a candidate for curative surgical resection.' This does not strictly align with the international guidelines (Northrup 2021). However, the applicant noted in further discussion that these criteria may be interpreted in a way as to not preclude first-line treatment with mTORi.

Though a greater than 3 cm AML diameter is typically described in the literature (Northrup 2021, Restrepo 2022, Gaur 2017, Amin 2018) as a guideline to indicate treatment rather than continued surveillance, in further discussion with the applicant, the applicant considered that treatment options for AML in TSC patients in practice are assessed on a case by case basis, with factors including: prior intervention, tumour size, tumour growth, other tumour characteristics, renal function, comorbidities and patient overall health.

Von Hippel-Lindau disease

Von Hippel-Lindau disease (VHL) is caused by germline mutations of the tumour suppressor gene *VHL*, located on the short arm of chromosome 3. While the majority of the affected individuals have a positive family history, up to 20% of cases arise from *de novo* mutations (Varshney 2017). It has an approximate incidence of 1 in 36000 live births (Maher 1991).

VHL is characterised by the abnormal growth of both benign and cancerous tumours and cysts in many parts of the body. Tumours usually first appear in young adulthood. Common manifestations include hemangioblastomas of the brain, spinal cord and retina, pheochromocytoma and paraganglioma, renal cell

carcinoma, pancreatic cysts and neuroendocrine tumours, and endolymphatic sac tumours (Varshney 2017).

Key clinical characteristics of VHL are presented in Table 7.

Table 7 Key clinical characteristics of VHL

Major features	Minor features
• Haemangioblastomas of the retina, spine or brain • ccRCC diagnosed <40 years of age or multiple/ bilateral ccRCC tumours diagnosed at any age • Adrenal paraganglioma • Paraganglioma of abdomen, thorax or neck • Retinal angiomas	• Endolymphatic sac tumours • Papillary cystadenomas of the epididymis or broad ligament • Pancreatic serious cystadenoma (>1) • Pancreatic neuroendocrine tumour or multiple pancreatic cysts (>1)

Source: NCCN guidelines 2021, Table 2, 'HRCC-A' page.
ccRCC = clear cell renal cell carcinoma

Based on the 2007 review of 573 VHL patients by Ong (2007), the lifetime risk (by age 70) of renal cell carcinoma (RCC) is up to 80%. However, this is likely to be an overestimate of risk as no adjustment was made for proband ascertainment (eviQ guidelines ID 397 v.7).

The National Comprehensive Cancer Network (NCCN) hereditary renal cell carcinomas guidelines (NCCN HRCC 2021 v1) recommended the following for patients with confirmed VHL related RCC:

- Management of localised renal masses typically guided under the 3 cm rule (Shuch 2012).
- The idea is to intervene at a time point of maximal benefit to the patient to limit the chance of development of metastatic disease but also to consider the recurrent and multiple resections many of these patients may have over the course of their lifetime with subsequent development of chronic and progressive renal failure.
- Patient should undergo partial nephrectomy if at all possible and consider referral to centres with surgical expertise in complex partial nephrectomies and management of VHL patients.
- Ablative treatment options may be considered for those with significant medical or surgical risk to undergo the operation.

In further discussion, the applicant noted that availability and utility of pharmacological options in VHL patients is a complex and evolving issue. The NCCN guidelines noted that pazopanib was associated with a greater than 50% objective response rate in renal lesions in a 31 patient phase II study. Pazopanib is currently only PBS reimbursed for the treatment of stage IV renal clear cell carcinoma.

Plon (2021) recommended that for patients who do not have bilateral nephrectomy or who have end stage kidney disease, tumour size and growth must be assessed:

- Patients with tumour of less than 3 cm diameter may continue surveillance or be treated with belzutifan, depending on growth of tumour and patient preference for more aggressive therapy.
- Patients with tumour size of 3 cm or more who are eligible for nephron sparing interventions, may require partial nephrectomy (preferred), or non-surgical options including cryotherapy, and radiofrequency ablation.
- Patients not eligible for nephron-sparing interventions may be treated with belzutifan.

PASC noted that belzutifan (HIF-2α inhibitor) received TGA orphan drug designation in February 2022. However, it is not PBS listed.

Birt-Hogg-Dubé syndrome:

Birt-Hogg-Dubé syndrome (BHD) is an autosomal dominant condition caused by a pathogenic variant in the folliculin (*FLCN*) gene. Patients with BHD may develop benign skin lesions, renal tumours and lung cysts leading to pneumothoraces. The incidence of BHD syndrome is unknown. Approximately 200 families have been identified worldwide (Menko 2009).

According to eviQ risk management guidelines, people with BHD have a 19% chance of developing kidney cancer over their lifetime (eviQ ID 161 v.61; Sattler 2018).

Hereditary papillary renal carcinoma (HPRC) - Type 1 Papillary renal carcinoma

Individuals with hereditary papillary renal carcinoma (HPRC) syndrome are at risk for the development of type 1 papillary renal cell carcinomas. Affected individuals in HPRC kindreds were found to be at risk for the development of bilateral, multifocal type 1 papillary renal carcinoma. Genetic studies in HPRC kindreds led to the identification of the *C-MET* gene on chromosome 7 as the gene for HPRC (Linehan 2009).

HPRC is considered to be rare. The number of people and families who have HPRC is unknown. However, there are approximately 30 families in published medical reports (Cancer.Net, 2020, HPRC).

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) - Type 2 Papillary renal carcinoma

Hereditary leiomyomatosis RCC (HLRCC) is a hereditary cancer syndrome in which affected individuals are at risk for the development of cutaneous and uterine leiomyoma and an aggressive form of type 2 papillary renal carcinoma. The gene for HLRCC has been found to be the Krebs cycle enzyme fumarate hydratase (*FH*).

The type 2 papillary kidney cancer found in HLRCC patients is a particularly aggressive form of renal carcinoma, i.e. it can metastasise early and is often fatal.

HLRCC is a rare condition that has been reported in approximately 300 families worldwide. Researchers suggest that it may be underdiagnosed (Medlineplus, HLRCC).

BAP1 tumour pre-disposition syndrome

BAP1 tumour predisposition syndrome (*BAP1*-TPDS) is associated with an increased risk for a specific skin lesion, *BAP1*-inactivated melanocytic tumours (BIMT; formerly called atypical Spitz tumours), and the following cancers, in descending order of frequency: uveal (eye) melanoma (UM), malignant mesothelioma (MMe), cutaneous melanoma (CM), renal cell carcinoma (RCC), and basal cell carcinoma (BCC) (Pilarksi 2016). Hepatocellular carcinoma, cholangiocarcinoma, and meningioma may also be associated with *BAP1*-

[1] https://www.eviq.org.au/cancer-genetics/consumer-information/3425-facts-for-people-and-families-with-birt-hogg#what-is-the-risk-of-cancer-and-other-features-of-b

TPDS. Affected individuals can have more than one type of primary cancer (Pilarksi 2016). In general, the median age of onset of these tumours is younger than in the general population.

Due to the limited number of families reported to date, the penetrance, natural history, and frequencies of *BAP1*-associated tumours are yet to be determined (Pilarski 2016).

Heterozygous *BAP1* germline pathogenic variants are specifically associated with an increased risk for RCC, in particular those with clear cell morphology (Haas & Nathanson 2014 cited in Pilarski 2016). Median age of RCC diagnosis appears to be younger in persons with *BAP1*-TPDS than in the general population (47-50 versus 64 years), and length of survival is decreased in persons with *BAP1*-related RCC (Rai 2016 cited in Pilarski 2016). Histology of these tumours is distinct from tumours not associated with pathogenic variants in *BAP1*, with higher grade at diagnosis and lack of somatic *PBRM1* pathogenic variants (which are common in RCC not associated with pathogenic variants in *BAP1)* (Peña-Llopis 2012 cited in Pilarski 2016).

Paragangliomas & phaeochromocytomas

Paragangliomas and phaeochromocytomas are not renal tumours but are rare neuroendocrine tumours. However, the syndromes described below are associated with an increased risk of renal tumours as well as paragangliomas or pheochromocytomas.

Phaeochromcytomas are tumours of the adrenal medulla, whereas paragangliomas arise from the extra-adrenal autonomic paraganglia, small organs consisting mainly of neuroendocrine cells that are derived from the embryonic neural crest and, like phaeochromocytomas, have the ability to secrete catecholamines (Young 2022). The majority of paragangliomas arise within the skull base and neck region.

The molecular pathogenesis of both sporadic and hereditary phaeochromocytoma and paraganglioma is incompletely understood. The majority of hereditary paragangliomas, particularly those arising in the skull base and neck, have been linked to pathogenic variants in the genes encoding different subunits of the succinate dehydrogenase (SDH) enzyme complex (Young 2022).

In addition, susceptibility to phaeochromocytomas and paragangliomas is an established component of four genetic syndromes: multiple endocrine neoplasia types 2A and 2B (MEN2), neurofibromatosis type 1 (NF1), von Hippel Lindau (VHL), and the Carney-Stratakis dyad.

Most cases of hereditary paraganglioma are accounted for by pathogenic variants in *SDHD*, *SDHB*, and *SDHC*, *VHL*, and *NF1* (Neumann cited in Young 2022).

Paraganglioma syndrome 4 (PGL4) is associated with pathogenic variants in *SDHB* at gene locus 1p36.1-35 and is the second most common type of familial paraganglioma. *SDHB* pathogenic variants are also associated with renal cell carcinoma (Young 2022).

Hereditary paraganglioma-phaeochromocytoma syndrome (HPPS) occurs in approximately 1 in 1 million people (Medlineplus HPPS).

Cowden syndrome

Cowden syndrome (CS) is an autosomal dominant hereditary cancer syndrome associated with increased risk of breast, thyroid, renal, uterine, and other cancers as well as benign neoplasms and neurodevelopmental concerns (Mester & Eng 2015). CS is the most common of the *PTEN* (phosphatase &

tensin homologue gene) hamartoma tumour syndromes (which include Bannayan-Riley-Ruvalcaba and Proteus-like syndromes).
Table 8 presents the lifetime risk of cancer/tumour in Cowden syndrome patients estimated in the eviQ risk management guidelines.

Table 8 Lifetime risk of cancer/tumour in PTEN/ Cowden syndrome patients from eviQ Guidelines

Cancer/tumour type	Risk for Cowden syndrome to age 70 years[a]	General population to age 70 years[b]
Breast (female)	High (uncertain but greater than 30% lifetime risk)	8%
Thyroid (mostly follicular sometimes papillary)	Increased (may be greater than 10%)[1]	0.87% (all types)
Endometrial	Increased (may be greater than 10%)	1.3% (uterine)
Renal	Increased (may be at least 10%)	0.82%
Melanoma	Unknown but possibly increased	3%
Colorectal	Unknown but possibly increased	2.5%

Source: eviQ Risk management guidelines ,ID: 546 v.9 o
[a] (Tan 2012; Bubien 2013; Nieuwenhuis 2013; Hendricks 2021)
[b] Australian Institute of Health and Welfare (AIHW) 2021 Cancer Data in Australia; Canberra: AIHW. https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancer-risk-data-visualisation opens in a new tab or window>. (2017 data)
Note: the published data on cancer risk has significant ascertainment bias

PASC noted that all the nominated syndromes were autosomal dominant, with patients diagnosed genetically, following development of tumours at an early age, or in patients having a family history of renal tumours or the genetic syndrome. However, PASC stated the syndromes were associated with variable penetrance and could arise due to de novo *variants and as a result, 'family history' was not a reliable indicator of risk.*

Table 9 presents the eviQ kidney-related surgical and surveillance recommendations for rare cancers arising from heritable pre-disposition syndromes.

Table 9 eviQ Guidelines surgical and surveillance recommendations for rare genetic cancers associated with renal cancer

Cancer syndrome Gene (and renal cancer type)	Recommendations	
VHL (RCC)	Surgical	• Multicentric and bilateral RCCs are common. Where possible, the management of renal cell carcinomas should be undertaken in a unit with expertise in nephron-sparing surgery.
	Surveillance	• Abdominal MRI 2 yearly with abdominal ultrasound in intervening years from age 10
FLCN BHD (Renal cancer)	Surgical	• Not described
	Surveillance	• Baseline abdominal MRI at age 20 years (Menko 2009; Schmidt & Lineman 2015; Houweling 2011) • If no abnormality then 3 yearly MRI or 2 yearly high resolution ultrasound, and continue for life (Lineman 2015) • The interval for follow up abdominal imaging for renal tumours <3 cm diameter is dependent on location and growth rate of tumours (Lineman 2015)
SDH (Renal cancer)	Surgical	• The care of affected individuals should be individualised based on their clinical situation
	Surveillance	• *SDHA*: 5 yearly starting at 18 years • *SDHB*: 2 yearly starting at 10 years • *SDHC*, *SDHD SDHAF2* (paternally inherited) : 3-5 yearly starting at 18 years • These recommendations coincide with MRI of base of skull to coccyx for PGL/PC • *SDHA* pathogenic variants demonstrate low penetrance. Few individuals with *SDHAF2* pathogenic variants have been reported, and penetrance is unclear. • Particular care should be taken in formulating follow-up plans for asymptomatic individuals with *SDHA* and *SDHAF2* pathogenic variants to avoid over-surveillance.
BAP-1 (renal cell carcinoma)	Surgical	• None described
	Surveillance	• Annual imaging ideally with MRI every 2 years alternating with high resolution renal ultrasound. If MRI not available, consider high resolution renal ultrasound annually
MET (Type 1 papillary renal cell carcinoma)	Surgical	• Risk-reducing surgery is not indicated • If tumours are detected, consider renal-sparing surgery if appropriate. This will depend on the size, location, growth rate, number of tumours and the patient's co-morbidities (Shuch 2012)
	Surveillance	• Baseline abdominal MRI at age 30 years. Consider high resolution ultrasound if MRI not available • If no abnormality, then 3 yearly imaging • The interval for follow up abdominal imaging for renal tumours <3 cm diameter is dependent on location and growth rate of tumours
FH *(*HLRCC-associated RCC)	Surveillance	• Annual abdominal MRI from age 18 years
	Surgical	• Surgical resection (with wide margin, or complete nephrectomy) if cancer is detected (due to aggressive nature and early metastasis)[2, 6]
PTEN (Renal cancer)	Surveillance	• Consider ultrasound 2 yearly from age 40 years
	Surgical	• None described

Source: eviQ Risk management guidelines (ID's 161v.6, 397 v.7, 546 v.9, 1657 v.5, 1658 v.5, 3558 v.3, 3928 v.1
BHD = Birt-Hogg-Dubé; MRI = magnetic resonance imaging; PGL/PCC = Hereditary paraganglioma-pheochromocytoma; RCC = renal cell carcinoma
Note: eviQ included recommendations across several organ systems. For concision, only the kidney-related recommendations are presented

PICO Set 2

Patients diagnosed with a syndrome associated with increased risk of kidney cancer (including TSC, Von Hippel-Lindau disease, Birt-Hogg Dubé syndrome, hereditary papillary renal carcinoma, hereditary leiomyomatosis and renal cell carcinoma, *BAP1*-TPDS, paraganglioma, Cowden syndrome, MiTF-*associated RCC, Lynch syndrome*) for the purposes of evaluating changes in clinical condition or suspected complications of known renal tumours arising between their annual surveillance MRI, or who have received disease specific therapeutic intervention.

For full description of these syndromes, see descriptions related to PICO Set 1 above.

Given that the TSC is substantially more common than the other syndromes, and that up to 80% of patients with TSC experience AML (Lee 2019, Kingswood 2016 cited in Restrepo 2022), it may be reasonable to expect that most patients accessing MRI for assessment of treatment response, will be those receiving treatment for TSC-related AML. For TSC patients, treatment response assessment would be expected three to six months after initiation of mTORi therapy (everolimus or sirolimus).

For patients with syndromes with a predisposition to malignant renal tumours, initial treatment may vary based on syndrome, as well as type, size and growth of the tumour. Treatment may include pharmacological options, if available, as well as minimally invasive procedures (radiofrequency ablation (RFA), cryoablation) and partial nephrectomy.

Prior testing

Patients accessing abdominal MRI for one of the syndromes above will have likely received prior genetic testing regardless of whether a pathogenic variant was detected.

The eviQ guidelines (1146 v.7) identified the following genes associated with kidney cancer for which positive test for a pathogenic variant would warrant referral to a family cancer clinic for assessment:

VHL, SDHB, MET, FLCN, FH, TSC1, TSC2, PTEN, MLH1, PMS2, MSH2, MSH6

The NCCN Guidelines Version 1 (2021) presented the following testing/ screening algorithm for patients with features or symptoms or clinical manifestations of heritable kidney cancer syndromes.

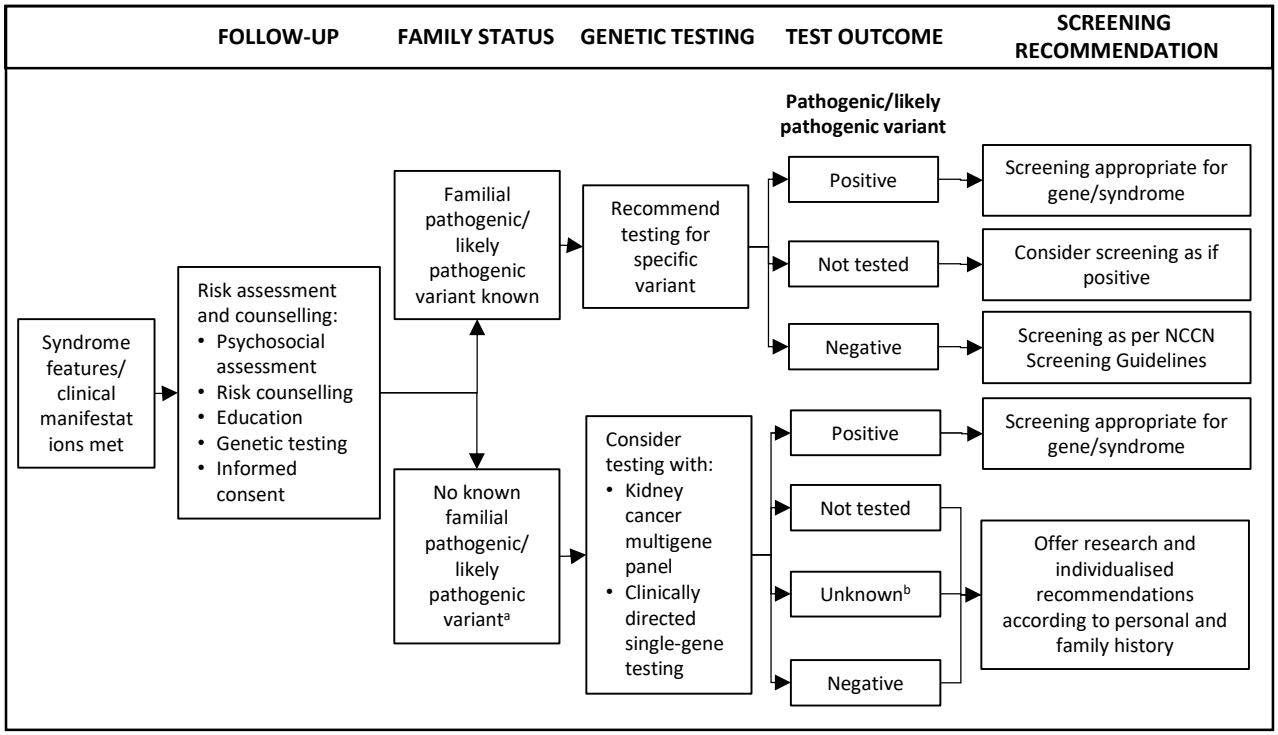

Figure 1 Testing/ screening algorithm for patients with features or symptoms or clinical manifestations of heritable kidney cancer syndromes adapted from the NCCN Guidelines (2021)

[a] in individuals who meet diagnostic criteria, but in whom no germline mutations are identified, consider workup for mosaicism

[b] variant of unknown significance (uninformative)

Genetic screening for heritable syndromes appears to constitute best practice both in Australia and internationally.

In the case of paragangliomas, biochemical confirmation of the diagnosis should be followed by radiological evaluation to locate the tumour, not the other way around (Stein & Black 1991, Bravo 1991, cited in Young 2022).

PASC considered that the prior tests be clarified for the PICO Sets:

PICO Set 1

- *Clinical diagnosis using standardised phenotypic diagnostic criteria.*
- *Genetic testing to confirm the presumptive phenotypic diagnosis, by presence of germline pathogenic or likely pathogenic variants or relevant genes.*

PICO Set 2

- *Previous abdominal imaging (US/CT/MRI) to identify renal tumours requiring treatment*
- *Biopsy/histopathology to confirm the morphological diagnosis of the tumour.*

Access to prior testing

It is expected that most patients with suspected inheritable conditions that are strongly associated with the development of renal tumours will not have access to MBS subsidised genetic testing for these mutations. It possible that testing may be accessed through state or institutional funding.

A small proportion of the requested population may have access to testing through the MBS. Specifically:

1) Whole exome sequencing for childhood syndromes (MBS item 73358) may identify some individuals with pathogenic variants in relevant genes.
2) Detection of the *VHL* Gene (MBS item 73333) is available for patients with:
    a. a clinical diagnosis of VHL and;
        i. a family history of VHL and one of the following:
            1. haemangioblastoma (retinal of CNS),
            2. phaeochromocytoma;
            3. renal cell carcinoma; or
        ii. two or more haemangioblastomas; or
        iii. one haemangioblastoma and a tumour or cyst of:
            1. the adrenal gland; or
            2. the kidney; or
            3. the pancreas; or
            4. the epididymis; or
            5. a broad ligament (other than epididymal and single renal cysts, which are common in the general population); or

b. in a patient presenting with one or more of the following clinical features suggestive of VHL syndrome:
   i. haemangioblastomas of the brain, spinal cord, or retina
   ii. phaeochromocytoma
   iii. functional extra-adrenal paraganglioma

3) Patients (Item 73296):
   i. with breast, ovarian, fallopian tube or primary peritoneal cancer; and
   ii. for whom clinical and family history criteria (as assessed, by the specialist or consultant physician who requests the service, using a quantitative algorithm) place the patient at greater than 10% risk of having a pathogenic or likely pathogenic gene variation identified in one or more of the genes *BRCA1, BRCA2, STK11, PTEN, CDH1, PALB2* and *TP53*; requested by a specialist or consultant physician.

Intervention

PICO Set 1

The application proposes Magnetic Resonance Imaging (MRI) of the abdomen using gadolinium-based contrast (where applicable) performed for the surveillance of patients with a confirmed clinical and/or molecular diagnosis of a condition known to carry an increased risk of the development of renal tumours who may or may not be undergoing active treatment.

The application states that following the establishment of a diagnosis of TSC or an inherited condition associated with increased risk of renal tumours, the patient would be reviewed by a clinician with expertise in managing patients with this condition. Baseline history and clinical examination will be performed.

A baseline (screening) abdominal MRI would be ordered by treating physician. The MRI would then be performed by a clinical radiology service and reported by a radiologist. In some circumstances where a patient may be unable to tolerate MRI scanning without sedation, they may be referred to a hospital service where MRI would be performed as an inpatient with appropriate sedation or anaesthesia.

For PICO Set 1, abdominal MRI is proposed for:
Regular screening for new (benign or malignant) lesions in patients diagnosed with a heritable rare kidney tumour syndrome.

In further discussion with the applicant, the applicant stressed the importance of assessing tumour growth in addition to tumour size in considering treatment options. Consequently, annual surveillance may require two separate abdominal MRI scans, three to six months apart, in order to survey for the size of tumours as well as the growth of such tumours. It was unclear how often two scans would be required, or whether this would only be required on the initial surveillance MRI. It is proposed that the response to treatment MBS item described for PICO Set 2 be expanded to be available for each new line of therapy, prior to commencement of therapy and 3-6 months post initiation of therapy, to assess the patient's response to treatment. As such, this item will be requested at clinician discretion, and will be restricted to no more than one scan every 3 month period.

Given that TSC, VHL and many other rare heritable syndromes associated with the development of renal tumours are associated with important health risks outside of the kidney which require management, abdominal MRI is proposed to be used in addition to other diagnostic and clinical procedures that constitute standard risk management for patients with these syndromes. Abdominal MRI constitutes one diagnostic tool in a wider approach of surveillance and management that may include other tests, including MRIs of other parts of the body.

Of note, was that the exclusive use of MRI is not unanimously recommended. In patients with VHL and *BAP1*, the eviQ guidelines specify that abdominal MRI should be done two yearly with ultrasound done in the intervening year. In DHB, the eviQ guidelines recommend either three yearly MRI or two yearly ultrasound if there are no abnormalities. In *PTEN*, ultrasound two yearly is recommended.

The VHL Alliance does not specify ultrasound in its active surveillance guidelines (VHL Alliance 2020), and is more consistent with the applicant's proposal.

Gaur (2017) considers that low dose CT continues to play an important role in surveillance as the disease may not be well characterised by MRI in all cases. A policy of alternating CT and MRI on serial surveillance imaging markedly reduces ionising radiation while benefiting from the complementary nature of CT and MRI.

Gaur (2017) also considers that surveillance is not recommended for HLRCC and SDHB, as these tumours are uniformly aggressive. Close surveillance (every year or every other year) is recommended in VHL, BHD, and TSC, whereas less intense surveillance is warranted in HPRC.

PASC agreed that current guidelines for surveillance (PICO Set 1) in this population were based on consensus; concluding that the existing guidelines are broadly in agreement with the need for the intervention but were not consistent with respect to detail (e.g., age at commencement, frequency and duration of surveillance).

The application notes that current legislative requirements stipulate that Medicare-eligible MRI items must be reported on by a trained and credentialed specialist in diagnostic radiology. The specialist radiologist must be able to satisfy the Chief Executive Medicare that they are a participant in the RANZCR Quality and Accreditation Program (Health Insurance Regulation 2013 – 2.5.4 – Eligible Providers; Australian Government 2013). The application considers that these legislative requirements will also apply to the proposed MRI item.

The application considers that for some paediatric patients and patients with neurological issues it is most appropriate that MRI be done under sedation. In these cases, where additional MRI scanning is required, for example brain MRI, these services would be delivered at the same time.

The application initially proposed that referrals for abdominal MRI in this population will be done by nephrologists, metabolic specialists, general physicians (i.e. general practitioner, or GP), or clinical geneticists. As part of the initial discussions with the applicant at an earlier stage of the application, they advised that in metropolitan centres nearly all patients are referred from a specialist or consultant physician in a tertiary setting, however in regional centres the patient may be referred by a GP. After further discussion with the applicant, they advised that consistent with most other MBS-listed MRI items,

the item descriptions for this application should specify that the service must be requested by a specialist or consultant physician, as patients under the primary care of a GP will have at least annual contact with a specialist. It was their view that for good clinical management and consistency with most other MBS-listed MRI items, the request should be made by a specialist/consultant physician.

The Ratified PICO confirmation for Whole Body MRI in *TP53* patients (MSAC 1668) specifies that service would be provided only in the context of a family cancer/genetics clinic, and be ordered by an appropriately trained clinician, expert in the management of hereditary cancers. The current application's specification may be broader than that ratified in the 1668 PICO.

PICO Set 2

Abdominal MRI is proposed under PICO Set 2 to:
Evaluate changes in clinical condition or suspected complications of known renal tumours arising between an annual surveillance MRI, or where a disease specific line of treatment has been initiated and an assessment of patient responsiveness to this treatment is required.

The application initially proposed that the MRI for assessing treatment response occur only once per lifetime. Further discussion with the applicant indicated that this is insufficient, and that in syndromes with both benign and malignant predispositions, once per new line of therapy may be necessary. Additionally, there will be a small group of patients who undergo a surveillance abdominal MRI and who due to a combination of features about their tumour/s (e.g. size of tumour and speed of growth), will require an evaluation of their clinical condition before their next annual surveillance MRI.

PASC noted that abdominal MRI could be undertaken using various sequences.

PASC considered advice should be sought from Royal Australian and New Zealand College of Radiologists (RANZCR) regarding a minimum acceptable dataset for MRI of renal tumours.

Comparators

The application considers that ultrasound, CT scans and no imaging are the appropriate comparators. In further discussions with the applicant, this was revised to ultrasound and CT scans. *PASC accepted the nominated comparators.*

Abdominal ultrasound is associated with MBS item 55036, and multiphase abdominal CT scans are associated with the MBS items 56047 and 56507.

In further discussions with the applicant, it was specified that ultrasound and CT scans would generally be replaced by MRI scans because abdominal MRI would be used instead of rather than in addition to these tests. However, it was noted that there may be instances where follow-up ultrasound might be useful after MRI.

PASC additionally discussed the advantages and disadvantages of US and CT, noting MRI (like US) does not utilise ionising radiation which is considered an important characteristic when used in a population predisposed to developing tumours and needing repeated assessments over time, but may require sedation or general anaesthetic for infants and young children or otherwise uncooperative patients.

Reference standard (for investigative technologies only)

In further discussion with the applicant and the Department of Health, biopsy and histopathology or computed tomography or ultrasound were considered appropriate reference standards.

PASC considered that biopsy and histopathology was the relevant reference standard for PICO Set 1.

PASC considered that biopsy and histopathology or computed tomography or ultrasound were appropriate reference standards for PICO Set 2.

Outcomes

PASC suggested amendments to some outcomes and clarified that some outcomes were relevant to only one PICO Set. These changes are noted in italicised text. The following outcomes are relevant to both PICO Sets, unless otherwise specified:

Safety outcomes:

- Adverse reaction to contrast agent.
- Cumulative effects of multiple contrast agent injections.
- Claustrophobia requiring the administration of sedation or general anaesthetic.
- Harms from follow-up testing.
- Other adverse events arising from MRI.
- Exposure to ionising radiation.

Effectiveness outcomes:

- Mortality.
- Time to diagnosis of tumours.
- Monitoring growth and number of tumours; relevant to PICO Set 1.
- Monitoring growth, complications or recurrence of tumours; relevant to PICO Set 2.
- Time from diagnosis to treatment.
- Assessing tumour response to treatment; relevant to PICO Set 2.
- Changes to management of treatment, for example:
  - use of mammalian target of rapamycin inhibitor (mTORi) therapy (TSC);
  - impacts on emergency presentations for spontaneous angiomyolipomas (AML) bleeding (TSC);
  - curative management (surgical and/or systemic cytotoxic therapy) for malignant tumours.
- Quality of life.

Test accuracy outcomes:

- Sensitivity and specificity compared to existing modalities.

Economic outcomes:

- Healthcare resources.
- Cost-effectiveness.
- Total Australian Government healthcare costs.

The application makes no claims regarding the value of knowing. *PASC questioned whether 'value of knowing' would be a relevant outcome.*

Assessment framework (for investigative technologies)

Exemplar approach

As noted under 'Population', patients with a number of different syndromes would be eligible for these services.

Given that TSC is substantially more frequent than the other syndromes for which listing is sought and that up to 80% of patients with TSC will have AML (Lee 2019, Kingswood 2016 cited in Restrepo 2022), and that evidence for these rare syndromes is generally sparse, it may be advisable to select TSC as an exemplar for assessment of effectiveness and cost-effectiveness of MRI in detecting benign kidney tumours associated with hereditary kidney tumour syndromes.

However, given that the treatment pathway for benign AML lesions differs substantially from that of malignant kidney tumours, it may also be advisable to select VHL, the next most common syndrome for which listing is sought, to serve as an exemplar for assessment in detecting malignant kidney cancers associated with hereditary kidney tumour syndromes.

It is acknowledged that syndromes with a predisposition to malignant tumours may also require treatment for benign tumours and vice versa. However, given the variety of distinct syndromes with distinct prognoses and treatment and a sparseness of evidence for these syndromes, a pragmatic distinction may be reasonable.

Assessment

No randomised trials were identified comparing MRI to CT or US in any of the requested populations. Consequently, a linked evidence approach may be required. However, a linked approach poses several challenges as well.

An initial search found no studies comparing the diagnostic accuracy of abdominal MRI to other modalities in detecting kidney tumours in TSC or VHL. The International TSC guidelines recommend MRI over CT based imaging, not on empirical comparisons but on the consideration that 25% to 30% can be fat poor and may be missed when abdominal ultrasonography is performed (Northrup 2021).

Further complicating assessment, Gaur (2017) considers that low dose CT continues to play an important role in surveillance as the disease may not be well characterised by MRI in all cases. A policy of alternating CT and MRI on serial surveillance imaging markedly reduces ionising radiation while benefiting from the complementary nature of CT and MRI.

In terms of estimating effect on health and clinical management, given that even within the more prevalent conditions of TSC and VHL, the applicant has stressed that assessment of treatment options specifically is made on the basis of several factors on a patient by patient basis, suggesting that accurately estimating effect on treatment management in practice will be challenging.

In terms of patient relevant outcomes, renal tumours are only one, important, clinical manifestation of syndromes that present across several organ systems. Thus, kidney health and even kidney tumour-specific

survival may be difficult to translate into health related quality of life and overall survival estimates, in the absence of randomised clinical trials.

For patients requiring MRI for the assessment of treatment response, there is a general sparseness of evidence across all of the kidney cancer syndromes. No comparative evidence was found in any of the cancer syndromes for MRI of the abdomen in assessment of response to treatment.

PASC noted that no comparative evidence between MRI and CT/US were identified in this patient population. PASC suggested that as diagnostic performance data (e.g., sensitivity and specificity) exist for MRI and the comparator imaging modalities in the sporadic (as opposed to genetic) forms of renal tumours, this could be used. PASC also considered there was no reason to suspect that these estimates would not be applicable to this population, but that this could be investigated in the assessment report.

Figure 2 presents an illustration of the assessment framework.

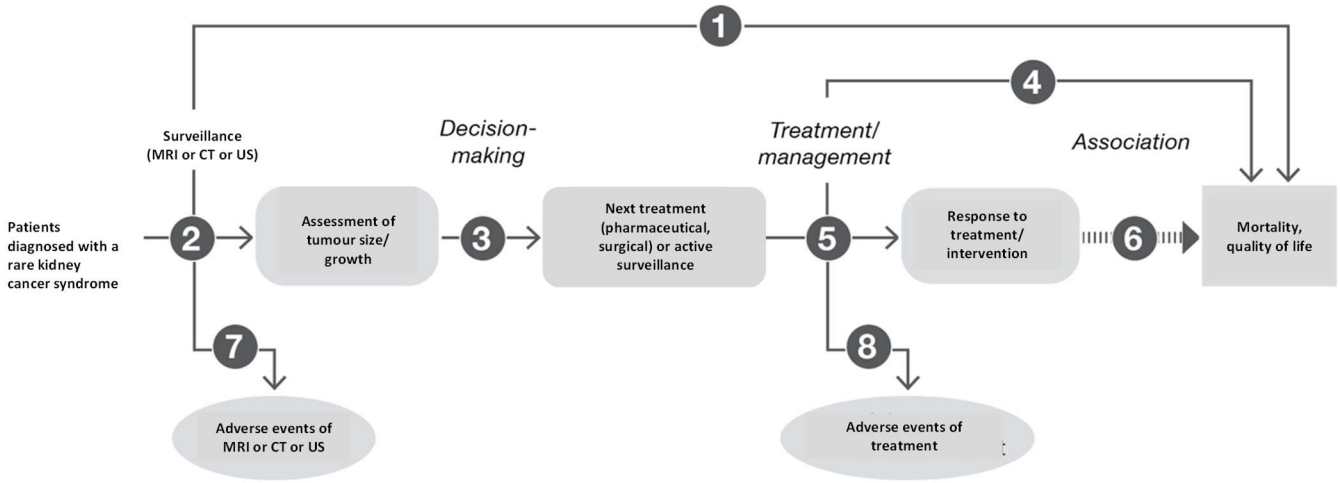

Figure 2 Assessment framework

Figure notes: 1: direct from test to health outcomes evidence; 2: test accuracy; 3: change in diagnosis/treatment/management; 4: influence of the change in management on health outcomes; 5: influence of the change in management on intermediate outcomes; 6: association of intermediate outcomes with health outcomes; 7: adverse events due to testing; 8: adverse events due to treatment

Clinical management algorithms

The application provides a current and proposed clinical management algorithm in p21 and p22 of the application, respectively. Amended current and proposed algorithms developed for the PICO Confirmation for the exemplar populations of TSC and VHL are presented in Figure 3 and Figure 4 respectively. *The algorithms capture further changes suggested by PASC.*

As discussed in the 'Assessment framework' section above, the exemplars do not necessarily reflect clinical management for other conditions, even those that share a tumour type (benign or malignant) predisposition with the exemplar population.

For example, Gaur (2017) notes that:

- For HLRCC and *SDHB* tumours, aggressive loco-regional surgery is recommended as these tumours tend to be locally invasive. Complete resection is the best chance for a long term survival and therefore, radical nephrectomy may be indicated.
- For the intermediate and low risk tumour types, emphasis is placed on nephron sparing techniques including robotic nephron sparing surgery and focal ablations. In this manner the tumours can be controlled while renal function is maintained for the maximal period. The risks associated with chronic dialysis or transplantation caused by overly aggressive surgical or ablative therapy can be nearly as high as the tumour itself so a balanced approach between treatment and active surveillance is warranted. In this regard, for the syndromes that pose intermediate and low risk, a threshold diameter of 3 cm for a solid renal tumour has proven successful in avoiding metastatic disease while spacing out surgical procedures so as to delay loss of renal function. This strategy has proven successful over a variety of hereditary conditions as will be described.

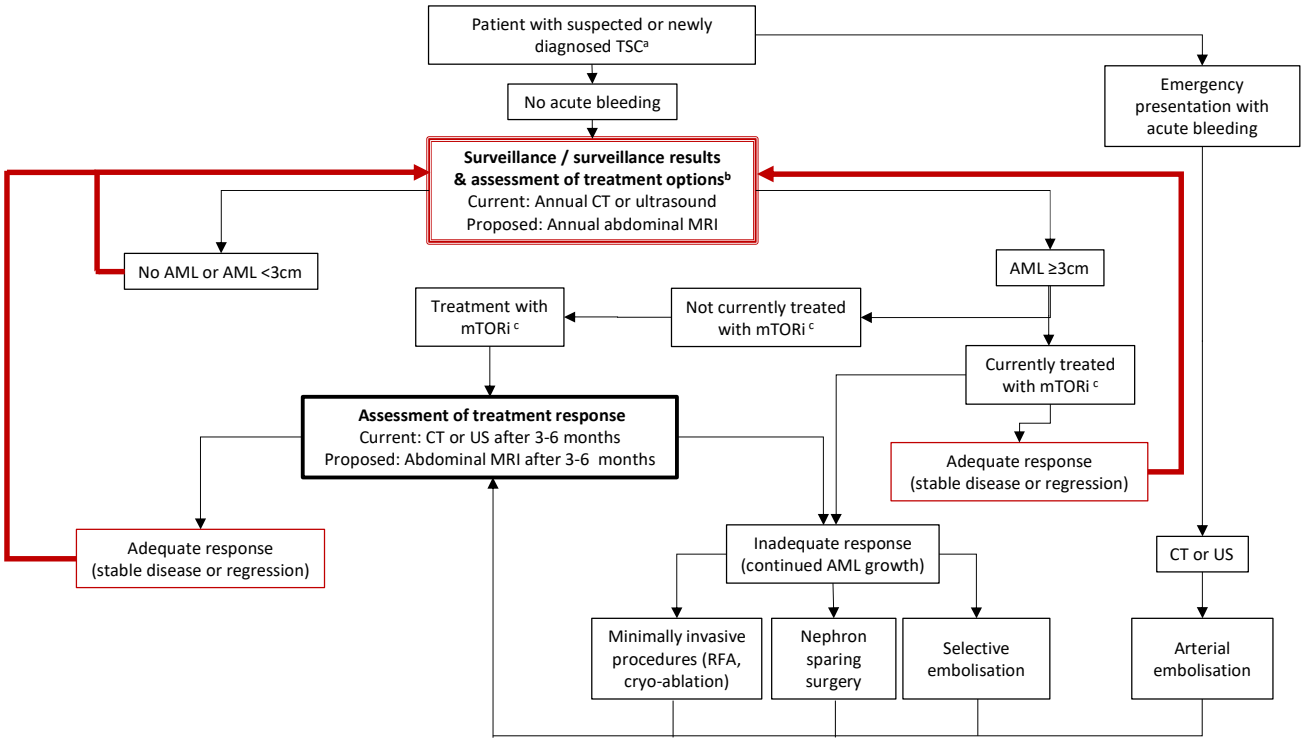

Figure 3 Current and proposed clinical management algorithm for patient with suspected or newly diagnosed TSC

Red lines depict that patients return to annual surveillance

[a] phenotypic or genetic diagnosis

[b] many factors besides tumour size may affect initial treatment for AML, and mTORi may not always be the appropriate first line therapy for tumours ≥3 cm. Likewise, surveillance may not always be the most appropriate option for patients with AML <3 cm. Tumour growth may also be a major factor. Consequently, in some cases, two CT, US or MRI tests 3 to 6 months apart may be appropriate to assess tumour growth.

[c] everolimus or sirolimus

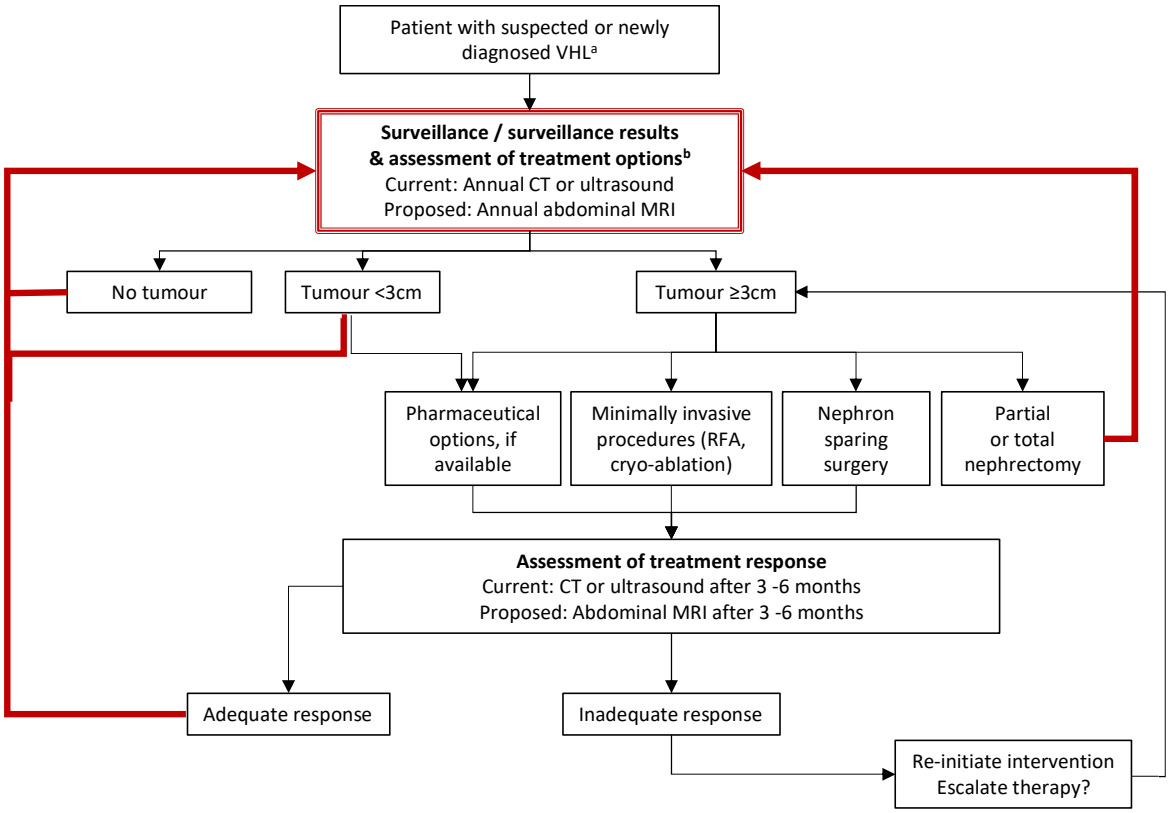

Figure 4 Current and proposed clinical management algorithm for patients with suspected or newly diagnosed VHL

Red lines depict that patients return to annual surveillance

[a] phenotypic or genetic diagnosis

[b] many factors besides tumour size may affect initial treatment for malignant tumours. Tumour growth may also be a major factor. Consequently, in some cases, two CT, US or MRI tests 3 to 6 months apart may be appropriate to assess tumour growth.

Proposed economic evaluation

Considering that the clinical claim is that abdominal MRI has superior effectiveness outcomes and superior safety outcomes relative to the comparators of CT scan or ultrasound, a cost effectiveness or cost-utility analysis would be appropriate. *PASC agreed that a cost-effectiveness or cost-utility analysis would be appropriate based on the clinical claim.*

Table 10 provides a guide for determining which type of economic evaluation is appropriate.

Table 10 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	**Uncertain[a]**	**Noninferior[b]**	**Superior**
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain[a]	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior[b]	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis
? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis
[a] 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations
[b] An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence

Proposal for public funding

PICO Set 1

The applicant proposes public funding for abdominal MRI for patients with a confirmed clinical and/or molecular diagnosis of those known to carry an increased risk of the development of renal tumours. The item descriptor in the application was as follows:

Category 5– Diagnostic Imaging Services
Magnetic Resonance Imaging using gadolinium-based contrast performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by a specialist (nephrologist or geneticist) or consultant physician scan of abdomen for patients aged under 85 years with a confirmed clinical and/or molecular diagnosis of a condition known to carry an increased risk of the development of renal tumours. Conditions include tuberous sclerosis complex, Birt-Hogg-Dube syndrome, Von Hippel Lindau syndrome, HLRCC, Cowden syndrome, *BAP1*-associated cancer syndrome and paraganglioma and other rare genetic disorders associated with increased risk of the development of renal tumours; And Maximum of once per year
Fee: $450 (MRI) and $120 (contrast agent)

Suggested amendments to the item descriptor are proposed as follows:

Category 5 – Diagnostic Imaging Services
MRI – scan of the abdomen, to assess the development and/or growth of renal tumours in patients with a confirmed clinical and/or molecular diagnosis of one of the following conditions: - Tuberous sclerosis complex - Von Hippel Lindau syndrome - Birt-Hogg-Dube syndrome - Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) - Cowden syndrome (*PTEN* Hamartoma Tumour Syndrome spectrum) - *BAP1*-associated cancer syndrome - *SDH* associated renal cancer (risk for phaeochromocytoma and paraganglioma) - Familial clear renal cell carcinoma with chromosome 3 translocation, or

other rare genetic disorders associated with the increased risk of developing renal tumours. For any particular patient – applicable not more than once in a 12 month period. *(R) (Anaes) (Contrast)* Bulk bill incentive **Fee:** $450.00 **Benefit:** 75% = $337.50 85% = $382.50

As discussed in the 'intervention section' above, the applicant stressed the importance of assessing tumour growth in addition to tumour size in considering treatment options. Consequently, annual surveillance may require two separate abdominal MRI scans, three to six months apart, for surveillance of the change in size of known tumours as well as the development of new tumours. It is proposed that the surveillance item remain applicable once in a 12 month period, and the response to treatment item also include an evaluation of changes in clinical condition for these patients, no more than once in a three month period.

The proposed fee is slightly lower than that of MBS listed MRI of the pelvis and abdomen for staging of cervical cancer (MBS Item 63473; Fee $627.20). The applicant did not provide justification for the proposed fee.

PICO Set 2

The application initially proposed abdominal MRI approximately three to six months after disease specific therapeutic intervention is initiated to assess responsiveness (once per lifetime). The item descriptor in the application was as follows:

Category 5– Diagnostic Imaging Services
Magnetic Resonance Imaging using gadolinium-based contrast performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by a specialist (nephrologist or geneticist) or consultant physician scan of abdomen for patients aged under 85 years with a confirmed clinical and/or molecular diagnosis of a condition known to carry an increased risk of the development of renal tumours. Conditions include tuberous sclerosis complex, Birt-Hogg-Dube syndrome, Von Hippel Lindau syndrome, HLRCC, Cowden syndrome (PTEN Hamartoma Tumour Syndrome spectrum), *BAP1*-associated cancer syndrome, SDH associated renal cancer (risk for phaeochromocytoma and paraganglioma) and familial clear renal cell carcinoma with chromosome 3 translocation, or other rare genetic disorders associated with increased risk of the development of renal tumours; And Approximately 3 - 6 months after disease specific therapeutic intervention is initiated to assess responsiveness (once per lifetime)
Fee: $450 (MRI) and $ 120(contrast agent)

Further discussion with the applicant also highlighted that there is a small group of patients who are not undergoing disease specific treatment but who will require subsequent evaluation of their clinical condition within the 12-month period of their surveillance MRI. Suggested amendments to the item descriptor are proposed as follows:

Category 5 – Diagnostic Imaging Services
MRI – scan of the abdomen, to assess response to treatment for a patient: a) with a confirmed clinical and/or molecular diagnosis of one of the following conditions: - Tuberous sclerosis complex - Von Hippel Lindau syndrome - Birt-Hogg-Dube syndrome - Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)

- Cowden syndrome (PTEN Hamartoma Tumour Syndrome spectrum)
- *BAP1*-associated cancer syndrome
- SDH associated renal cancer (risk for phaeochromocytoma and paraganglioma)
- Familial clear renal cell carcinoma with chromosome 3 translocation, or
- other rare genetic disorders associated with the increased risk of developing renal tumours, and

b) for the purposes of evaluating changes in clinical condition or suspected complications of known renal tumours arising between an annual surveillance MRI claimed under item INSERT NUMBER FOR ITEM ABOVE; or

c) where a disease specific line of treatment has been initiated and an assessment of patient responsiveness to this treatment is required

For any particular patient – applicable not more than once in a 3 month period. *(R) (Anaes) (Contrast)*

Bulk bill incentive

Fee: $450.00 **Benefit:** 75% = $337.50 85% = $382.50

Further discussion with the applicant indicated that in kidney cancers with both benign and malignant predispositions, abdominal MRI once per new line of therapy may be necessary. This has been reflected in the changes above.

The proposed fee is slightly lower than that of MBS listed MRI of the pelvis and abdomen for staging of cervical cancer (MBS Item 63473; Fee $627.20). The applicant did not provide justification for the proposed fee.

PASC discussed the proposed item descriptors and suggested changes be made for clarity, noting a preference for the proposed item descriptor for PICO Set 2 that was set out by the Department and developed with the applicant.

- *PASC discussed the requirement for 'in consultation with geneticist' for eligibility in the proposed item descriptors tabled by the Department. The applicant stated that geneticists are largely not involved in the management of patients with TSC. PASC indicated that alternative wording should be explored.*
- *PASC noted the fee structure was not consistent with existing fee structures for MRI and either needed to be aligned or justified. The applicant will advise the fee structure they intend to proceed with, in line with existing and similar MRI items listed in the MBS which use gadolinium-based contrast, such as MRI of the abdomen and pelvis for cervical cancer.*
- *PASC suggested as an alternative to listing all eligible conditions in the item descriptors that they refer to 'a genetic disorder associated with an increased risk of developing renal tumours' with an explanatory note to either specify eligible conditions or refer to 'rare genetic disorders associated with a >N% risk of developing renal tumours' (where the value of the risk threshold N% would be specified).*

Separate contrast item

The applicant has advised that contrast would be used for most scans, excepting those where it is contraindicated on the usual criteria (eGFR<30ml/min/1.73m^2; non-compatible medical device *in situ*; metallic foreign body *in situ,* etc). It would be an option to list the contrast as a separate item, consistent

with the MBS listing of Liver MRI (63545, 63546, 63496). The contrast item can be used with both proposed MBS (surveillance and staging/response) items as required, see below.

Category 5 – Diagnostic Imaging Services
NOTE: Benefits in Subgroup 22 are only payable for modifying items where claimed simultaneously with MRI services. Modifiers for sedation and anaesthesia may not be claimed for the same service. MRI service to which item XXX or XXX applies if: (a) the service is performed on a person under the supervision of an eligible provider; and (b) the service is performed using a gadolinium based specific contrast agent. Bulk bill incentive **Fee:** $120.00 **Benefit:** 75% = $90.00 85% = $102.00

Summary of public consultation input

Consultation feedback was received from five [5] professional organisations, two [2] consumer organisations and ten [10] individuals, all care givers. The seven [7] organisations that submitted input were:

- Australian and New Zealand Society of Nephrology (ANZSN)
- Australian Society of Medical Imaging and Radiation
- Kidney Health Australia
- Royal Australian and New Zealand College of Radiologists (RANZCR)
- Royal College of Pathologists of Australasia (RCPA)
- Tuberous Sclerosis Australia (TSA)
- Urological Society of Australia and New Zealand (USANZ)

The consultation feedback received was all supportive of public funding for MSAC application 1702. The RANZCR considered that the proposed service is evidence-based and clinically appropriate for the surveillance of patients with rare genetic conditions associated with the increased risk of renal tumours.

Clinical need and public health significance

The main benefits of public funding received in the consultation feedback included:

- superior imaging sensitivity and specificity for early detection and characterisation of renal tumours with MRI screening
- earlier and more accurate diagnosis and resulting targeted therapy, which can improve disease outcomes and extend life, and
- increased equity of access.

The TSA noted that MRI is the only effective method to detect fat-poor angiomyolipomas (AMLs) in patients living with Tuberous Sclerosis Complex (TSC). It pointed out that the cost of MRIs prohibited some of their members from undertaking the regular screening privately, or alternatively face an out-of-pocket cost between $400 to $600 per screening.

The main disadvantages of public funding received in the consultation feedback included the limited capacity of diagnostic radiology. One response noted that this may result in a potential disadvantage to the health system, and the other considered that patients may encounter long waiting lists due to limited capacity of MRI services.

The consultation feedback identified other services needed to be delivered before or after the intervention, including:

- diagnostic genetic testing utilising MBS item numbers
- genetic counselling both for patients and their family members
- education and evidence-based guidelines for kidney clinicians on the new service.

Indication(s) for the proposed medical service and clinical claim

The consultation feedback ranged from 'strongly agreeing' to 'agreeing' with the proposed population(s).

- The RCPA noted that the following genetic conditions / pathogenic variants should be included in the population:
    - Beckwith Wiedemann syndrome
    - WT1 pathogenic variants
    - Uniparental disomy (UPD)- chromosome 11
    - Copy number variations (CNVs) of that area of chromosome 11
    - CDKN1C pathogenic variants.
      *However, PASC noted that these variants are associated with predisposition to nephroblastoma (Wilms tumour) in infancy and childhood, for which the current recommendation for surveillance is US (Kalish JM et al: Clin Cancer Res 2017; **23**:e115-e122).*
- The USANZ considered that inclusion of additional relevant syndromes should be clarified (e. g. hereditary papillary type 1 RCC, SDH-srRCC), and also coverage for additional new conditions with an increased risk of renal cancers that may be identified in the future. It also noted that urologist should be included in the referring specialists.
- The TSA noted that children with TSC who require sedation for MRI, should be able to combine an abdominal MRIs with their regular brain MRIs.

The consultation feedback ranged from 'strongly agreeing' to 'agreeing' with the proposed comparator(s) and the clinical claim. Consultation feedback considered that MRI would be best imaging technique for recurrent screening, as small lesions may be missed on ultrasound; serial monitoring of growth is more accurate on cross sectional MRI imaging; and cumulative radiation dose from recurrent computerized tomography (CT) scans is significant.

Cost information for the proposed medical service

The consultation feedback ranged from 'strongly agreeing' to 'agreeing' with the proposed service descriptor and proposed fee.

The RANZCR considered that it should be clarified that radiologists would be the providers of the service rather than nephrologists. Kidney Health Australia considered that the proposed fees should be reviewed against current charges from public and private services, and out of pocket cost should be minimised.

Individual Feedback

Ten individual submissions were received from caregivers of children with tuberous sclerosis complex (TSC), which all supported the application.

The consumers considered that abdominal MRIs would lead to earlier detection and treatment of tumours, and better health outcomes and are recommended in international guidelines for screening of tumours. Some feedback considered that it would be helpful to combine abdominal MRIs with brain MRIs, where patients require sedation for their MRI.

The feedback considered that public funding of abdominal MRIs would ensure equity of access and pointed out the significant cost of caring for a family member with TSC, where many are unable to afford privately funded abdominal MRIs.

*PASC discussed the responses from six organisations. All were supportive of the proposal. PASC noted that RANZCR clarified that radiologists and not nephrologists were providers of the service. PASC also noted that the Royal College of Pathologists of Australia suggested that other rare conditions which could also be included in the population include: Beckwith Wiedemann syndrome (*WT1 *would be another gene), UPD chromosome 11, CNVs of that area of chromosome 11,* CDKN1C *pathogenic variants; however, these variants are associated with predisposition to nephroblastoma (Wilms tumour) in infancy and childhood, for which the current recommendation for surveillance is US (Kalish JM et al: Clin Cancer Res 2017;* ***23****:e115-e122).*

PASC noted there were also more than 10 individual responses; all were from individuals who had, or were parents of people who had, TSC. All responses were also supportive.

Next steps

The applicant indicated the assessment would proceed as a Department Contracted Assessment Report (DCAR).

Applicant comment on ratified PICO Confirmation

Access to prior testing

Following the outcome of MSAC Application No. 1600, genetic testing for heritable kidney disease will be available through the MBS as of 01/07/22, therefore the section "Access to Prior Testing" will no longer be

accurate. This does not have a substantial impact on this application for abdominal MRI funding, only on the availability of reimbursed prior testing.

Proposal for public funding

As discussed in PASC the applicant agrees the fee should be aligned with existing abdominal MRI MBS item numbers to reflect current costs of this service – this relates to item number 63473 - $627.20 and item number 63491 - $44.80

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