



Australian Government
Department of Health

Application 1702

Abdominal MRI for rare genetic conditions associated with increased risk of renal tumours

This application form is to be completed for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)). It describes the detailed information that the Australian Government Department of Health requires to determine whether a proposed medical service is suitable.

Please use this template, along with the associated [Application Form Instructions](#) to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted. The separate [MSAC Guidelines](#) should be used to guide health technology assessment (HTA) content of the Application Form

Should you require any further assistance, departmental staff are available through the Health Technology Assessment Team (HTA Team) on the email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

Email: hta@health.gov.au

Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant): Rare Voices Australia

Corporation name: Rare Voices Australia

ABN: 69 156 254303

Business trading name: Rare Voices Australia

Primary contact name: REDACTED

Primary contact numbers

Business: REDACTED

Mobile: REDACTED

Email: REDACTED

Alternative contact name: REDACTED

Alternative contact numbers

Business REDACTED

Mobile REDACTED

Email REDACTED

2. (a) Are you a consultant acting on behalf on an applicant?

- Yes
 No

(b) If yes what is the Applicant(s) name that you are acting on behalf of?

Not applicable

3. (a) Are you a lobbyist acting on behalf of an Applicant?

- Yes
 No

(b) If yes, are you listed on the Register of Lobbyists?

- Yes
 No

(c) Have you engaged a consultant on your behalf?

- Yes
 No

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

4. Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words)

Abdominal MRI for rare genetic conditions associated with increased risk of renal tumours

A number of rare defined genetic conditions are strongly associated with the development of renal tumours over time. This includes (not is not limited to) Tuberous Sclerosis Complex (TSC), Von Hippel-Lindau disease, Birt-Hogg –Dube syndrome, hereditary leiomyomatosis and renal cell cancer (HLRCC), Cowden syndrome, BAP1-associated cancer syndrome and paraganglioma. The commonest condition in this group of disorders is Tuberous Sclerosis Complex (TSC) and is characterized by the growth of benign tumours in multiple organs that occur as the result of a loss of function mutation in one to the two TSC genes leading to the over activity of mammalian target of rapamycin (mTOR) pathway. 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. Approximately 70% of patients with TSC develop angiomyolipomas (AML) of the kidneys.

A number of defined genetic conditions are strongly associated with the development of renal tumours over time. In asymptomatic patients who have been diagnosed with one of these conditions, regular screening for renal lesions is recommended in treatment guidelines. Screening enables earlier diagnosis of tumours at a stage when these are still amenable to curative intervention. The commonest condition in this group of disorders is Tuberous Sclerosis Complex (TSC), for which the need for renal surveillance is shared with Von Hippel Lindau and Birt Hogg Dube syndromes, and with the rarer HLRCC, Cowden syndrome, BAP1-associated cancer syndrome and paraganglioma.

These inheritable conditions are together responsible for about 4% of all renal tumours (Linehan WM, Zbar B, Klausner RD. Renal carcinoma. In: Scriver CR, Beaudet AL, Sly WS, et al., eds. The Metabolic and Molecular Bases of Inherited Disease. New York: McGraw-Hill, 2001: 907–29.)

5. Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)

Magnetic Resonance Imaging (MRI) of the abdomen using gadolinium-based contrast 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.

MRI allows for early detection and treatment of tumours, thereby improving outcomes for those diagnosed with these rare conditions.

6. (a) Is this a request for MBS funding?

Yes

(b) If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?

Amendment to existing MBS item(s)
 New MBS item(s)

(c) If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service/technology:

Not applicable

(d) If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?

Not applicable

(e) If a new item(s) is being requested, what is the nature of the change to the MBS being sought?

- i. A new item which also seeks to allow access to the MBS for a specific health practitioner group
- ii. A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new population)
- iii. A new item for a specific single consultation item
- iv. A new item for a global consultation item(s)

(f) Is the proposed service seeking public funding other than the MBS?

No

(g) If yes, please advise: N/A

NA

7. What is the type of medical service/technology?

- Therapeutic medical service
- Investigative medical service
- Single consultation medical service
- Global consultation medical service
- Allied health service
- Co-dependent technology

8. For investigative services, advise the specific purpose of performing the service (which could be one or more of the following):

- i. To be used as a screening tool in asymptomatic at-risk populations
- ii. Assists in establishing a diagnosis in symptomatic patients
- iii. Provides information about prognosis
- iv. Identifies a patient as suitable for specific therapy by predicting a variation in the effect of the therapy
- v. Monitors a patient over time to assess treatment response and guide subsequent treatment decisions

9. Does your service rely on another medical product to achieve or to enhance its intended effect?

- Pharmaceutical / Biological
- Prosthesis or device
- No

10. (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?

No

(b) If yes, please list the relevant PBS item code(s):

Not applicable

(c) If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?

No

(d) If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?

Not applicable

11. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List?

Not applicable

(b) If yes, please provide the following information (where relevant):

Not applicable

(c) If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses List Advisory Committee (PLAC)?

No

(d) Are there any other sponsor(s) and / or manufacturer(s) that have a similar prosthesis or device component in the Australian marketplace which this application is relevant to?

No

(b) If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s):

Not applicable

12. Please identify any single and / or multi-use consumables delivered as part of the service?

Single use consumables: Intravenous gadolinium is used in most MRI procedures, unless precluded by the patient's eGFR being <30 ml/min in which case a contrast agent would not be used. This will require the creation of a modifying MBS item which is to be claimed simultaneously with the proposed MRI item.

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

13. (a) If the proposed medical service involves use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer, or any other type of therapeutic good, please provide details.

The proposed services requires use of a MRI Scanner and a gadolinium contrast based agent. Both technologies are currently listed on the ARTG.

- (b) Has it been listed on the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)? If the therapeutic good has been listed on the ARTG, please state the ARTG identification numbers, TGA-approved indication(s), and TGA-approved purpose(s).

Yes

14. Gadovist (Bayer) ARTG Identification numbers: 72518, 72517, 72494, 72493, 67046, 67047, 67048, and 286854

Contrast enhancement in whole body MRI including head and neck region, thoracic space, breast, abdomen (pancreas, liver and spleen), pelvis (prostate, bladder and uterus), retroperitoneal space (kidney), extremities and musculoskeletal system

- (c) If a medical device is involved, has the medical device been classified by TGA as a Class III OR Active Implantable Medical Device (AIMD) under the TGA regulatory scheme for devices?

Class III

AIMD

N/A

- (d) Is the therapeutic good classified by TGA for Research Use Only (RUO)?

No

15. (a) If not listed on the ARTG, is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*? N/A

Not applicable

- (b) If the therapeutic good is not ARTG listed, is the therapeutic good in the process of being considered by TGA?

Not applicable

- (c) If the therapeutic good is NOT in the process of being considered by TGA, is an application to TGA being prepared?

Not applicable

PART 4 – SUMMARY OF EVIDENCE

16. Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology.

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
1.	Review of TSC	Renal disease in tuberous sclerosis complex: pathogenesis and therapy	<p>Key points:</p> <ol style="list-style-type: none"> 1.RCC occurs in ~2–4% of patients with TSC 2. The median age of onset of RCC is two decades earlier in patients with TSC than in the general population 3. RCC can develop in young children and even infants with TSC 4. Multiple bilateral RCCs can develop in the same patient 5. Routine imaging frequently identifies early RCCs, allowing for nephron-sparing therapy 	https://www.nature.com/articles/s41581-018-0059-6	19 September 2018
2.	Delphi Consensus guidelines from 51 TSC experts	Amin et al The UK Guidelines for management and surveillance of TSC	<ol style="list-style-type: none"> 1.MRI should be performed at diagnosis, regardless of age, to assess presence of AMLs, renal cysts and RCCs. MRI is the optimal imaging modality as some lesions, including fat-poor AMLs, can be overlooked on ultrasound. 2.All patients with TSC should have regular imaging every 1-2 years 3.Enlarging AMLs >3cm should be treated with mTORi 	https://academic.oup.com/qjmed/article/112/3/171/5104881?login=true	2019
3.	RCT	Bissler et al Everolimus for angiomyoipomata associated with TSC	Everolimus decreased AML volume with an acceptable safety profile	https://www.sciencedirect.com/science/article/pii/S014067361261767X	2013

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
4.	Consensus Guidelines	Northrup H, Aronow ME, Bebin EM, Bissler J, Darling TN, de Vries PJ, Frost MD, Fuchs Z, Gosnell ES, Gupta N, Jansen AC. Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations. Pediatric Neurology. 2021 Oct 1;123:50-66.	<p>-abdominal imaging should be obtained at the time of diagnosis, regardless of age, and repeated every 1-3 yrs throughout the patient's lifetime. Annual scans recommended for tumours approaching 3cm in size and/or are growing.</p> <p>-MRI is preferred modality for evaluation of angiomyolipomata – because 25-30% are fat poor and may be missed in abdominal CT or US</p> <p>- abdominal MRI may be combined with brain MRI if anaesthesia is needed.</p> <p>-MRI of the abdomen may reveal aortic aneurysms or extrarenal hamartomas of the liver and neuroendocrine tumors in the pancreas and other abdominal organs that also can occur in individuals with TSC.</p>	https://www.sciencedirect.com/science/article/pii/S088789942100151X?via%3Dihub	October 2021
5	Review	Trnka and Kennedy Renal tumors in tuberous sclerosis complex	<p>Renal AML develop in 80% of people with tuberous sclerosis complex (TSC) by adulthood.</p> <p>Risk of haemorrhage increases as AML increase in size above 3 cm in diameter.</p> <p>All children with TSC should undergo regular surveillance with kidney imaging</p> <p>mTOR inhibitors are effective in reducing growth and size of AML in patients with TSC.</p>	https://ern-ithaca.eu/wp-content/uploads/2020/12/Trnka_TS_kidney_PediatrNephrol2020.pdf	2020

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
6	Clinical guidelines developed by multidisciplinary expert team	eviQ	-guidelines recommend MRI risk management for people with genetic disorders that carry increased risk of renal cancer	https://www.eviq.org.au/cancer-genetics/adult/risk-management/161-flcn-birt-hogg-dube-risk-management#cancer-tumour-risk-management-guidelines https://www.eviq.org.au/cancer-genetics/adult/risk-management/1657-fh-hereditary-leiomyomatosis-and-renal-cell#cancer-tumour-risk-management-guidelines	Krueger and northrup
7	Cross-sectional retrospective analysis	Johannes et al. (2019) Renal imaging in 199 Dutch patients with Birt-Hogg-Dubé syndrome:	Of 121 patients screened at diagnosis then followed for a mean of 4.2 yrs, 32 renal cancers were found in 23 patients. Nine small tumours (7-27mm) were missed on ultrasound but seen on MRI or CT.	https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0212952	2019
8	Analysis of 130 solid renal tumours removed from 30 BHD patients from 19 families, all screened	Pavlovich CP et al Renal Tumors in the Birt-Hogg-Dubé Syndrome,	<p>Malignant propensity increased with tumour size – hybrid tumours average 2.2cm; chromophobe Ca 3.0cm, clear cell 4.7 cm. Types commonly existed together, and present bilaterally.</p> <p>THEREFORE – optimal screening modality should have resolution to 1-2cm, AND intervention needs to spare nephrons</p>	https://journals.lww.com/ajsp/Fulltext/2002/12000/Optimal_Histopathologic_Examination_of_the.2.aspx#O8-2-3	December 2002

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
9	Interdisciplinary review	Schmid et al Management of Von-Hippel landau disease: an interdisciplinary review	- The most frequent malignant tumour entity in VHL disease is ccRCC - active surveillance with MRI is recommended in tumours below 3 cm, as early surgical removal may deteriorate renal function. Adherence to a strict surveillance protocol is necessary to minimize metastatic risk.	https://www.karger.com/Article/Fulltext/369362	2014
10	Lit review	Maher Hereditary Renal Cell Carcinoma Syndromes: diagnosis, surveillance and management	- inherited forms of RCC including Von Hippel Landeau disease, Birt-Hogg-Dube syndrome, Hereditary Leiomyomatosis, chromosome 3 translocations, and mutations in BAP1 have high risk of developing RCC -principal strategy for preventing morbidity and mortality in individuals at risk of inherited RCC is detection of early stage tumours	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6280834/	2018
11	Case series of VHL patients studied with uniform novel protocol	Vanbinst AM, Brussaard C, Vergauwen E, Van Velthoven V, Kuijpers R, Michel O, Foulon I, Jansen AC, Lefevre B, Bohler S, Keymolen K. A focused 35-minute whole body MRI screening protocol for patients with von Hippel-Lindau disease. Hereditary cancer in clinical practice. 2019 Dec;17(1):1-6.	Annual or biennial MRI screening is recommended in VHL patients, but rather than separate abdominal, brain and spine studies, these may be combined in a 35 minute whole body MRI study	https://hccjournal.biomedcentral.com/articles/10.1186/s13053-019-0121-9	29 July 2019

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
12	Review VHL	Varshney N, Kebede AA, Owusu-Dapaah H, Lather J, Kaushik M, Bhullar JS. A review of Von Hippel-Lindau syndrome. Journal of kidney cancer and VHL. 2017;4(3):20.	Age >16 yrs - Ultrasound and MRI scan of the abdomen with and without contrast to assess kidneys, pancreas, and adrenals is recommended at least every other year. Renal cancers preset at average age 39 (16-67) and occur in 30-70% of patients.	https://rq2fy6yp4u.scholar.serialssolutions.com/?sid=google&auinit=N&aualast=Varshney&atitle=A+review+of+Von+Hippel-Lindau+syndrome&id=pmid:28785532	2 Aug 2017

17. Identify yet-to-be-published research that may have results available in the near future (that could be relevant to your application). Do not attach full text articles; this is just a summary.

None identified

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

- 18. List all appropriate professional bodies/organisations representing the health professionals who provide the service. For MBS-related applications ONLY, please attach a brief ‘Statement of Clinical Relevance’ from the most relevant college/society.**

Australian and New Zealand Society of Nephrology

- 19. List any professional bodies / organisations that may be impacted by this medical service (i.e. those who provide the comparator service):**

Human Genetics Society of Australasia

Royal Australasian College of Physicians

Urological society of Australia and New Zealand

Royal Australian and New Zealand College of Radiologists

- 20. List the consumer organisations relevant to the proposed medical service (noting there is NO NEED to attach a support letter at the ‘Application Lodgement’ stage of the MSAC process):**

Tuberous Sclerosis Australia

Rare Voices Australia

Kidney Health Australia

Rare Cancers Australia

- 21. List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:**

N/A

- 22. Nominate two experts that can be contacted about the proposed medical service, and current clinical management of the condition:**

Name of expert 1: **REDACTED**

Telephone number(s) **REDACTED**

Email address: **REDACTED**

Justification of expertise: **REDACTED**

Name of expert 2: **REDACTED**

Telephone number(s): **REDACTED**

Email address: **REDACTED**

Justification of expertise: **REDACTED**

PART 6 – POPULATION (AND PRIOR TESTS), INTERVENTION, COMPARATOR, OUTCOME (PICO)

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

23. Define the medical condition, including providing information on the natural history of the condition and a high level summary of associated burden of disease (in terms of both morbidity and mortality):

Tuberous Sclerosis Complex (TSC) is a multisystem hereditary disorder with an incidence of approximately 1:6000 live births. It is characterized by the growth of benign tumours in multiple organs that occur as the result of a loss of function mutation in one to the two TSC genes leading to the over activity of mammalian target of rapamycin (mTOR) pathway. 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.

Approximately 70% of patients with TSC develop angiomyolipomas (AML) of the kidneys. With 21-40% of all people with TSC experiencing bleeding from AMLs or chronic kidney disease. 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 PBS in Australia for the treatment of visceral tumours associated with TSC.

According to Tuberous Sclerosis Australia TSC has an incidence 1:6,000 and prevalence of 8.8:100, 000 in Australia.

Other rare syndromes with increased risk of renal tumors

These may include but are not limited to example Von Hippel-Lindau disease, Birt-Hogg –Dube syndrome, hereditary leiomyomatosis and renal cell cancer (HLRCC), Cowden syndrome, BAP1-associated cancer syndrome and paraganglioma. (**Von Hippel-Lindau (VHL) disease** is an inherited disorder with an approximate incidence of 1 in 36,000 live births. It is characterized 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. Abdominal MRI is recommended at least every other year. REF Varshney et al, 2017. **Birt-Hogg-Dubé (BHD) syndrome** is a rare complex genetic skin disorder (genodermatosis) characterized by the development of skin papules generally located on the head, face and upper torso. These benign (noncancerous) tumours (hamartomas) of the hair follicle are called fibrofolliculomas. BHD syndrome also predisposes individuals to the development of benign cysts in the lungs, repeated episodes of a collapsed lung (pneumothorax), and increased risk for developing kidney neoplasia. **Hereditary leiomyomatosis and renal cell cancer (HLRCC)** is a condition that causes benign tumours of smooth muscle tissue in the skin (cutaneous leiomyomas) and in the uterus in females (uterine leiomyomas, or fibroids). The condition also increases the risk of kidney cancer. About 10% to 16% of people with HLRCC develop renal cell cancer; symptoms of this cancer may include lower back pain, blood in the urine, and/or a mass in the kidney that can be felt by a physician. Some people have no symptoms until the cancer is advanced. HLRCC is caused by mutations in the [FH](#) gene and is inherited in an autosomal dominant manner. **PTEN hamartoma tumour syndrome (PHTS, Cowden syndrome)** is a spectrum of disorders caused by mutations of the *PTEN* tumour suppressor gene in egg or sperm cells (germline). These disorders are characterized by multiple hamartomas that can affect various areas of the body. Hamartoma is a general term for benign tumour-like malformation composed of mature cells and tissue

normally found in the affected area that have grown in a disorganized manner. Individuals with a variety of clinical diagnoses who ultimately have been found to carry a germline *PTEN* mutation as the underlying cause are said to have PHTS. *PTEN* can activate mTOR, and mTOR inhibitors are used if renal cancer develops. Renal cancer is less common than breast cancer (lifetime risk up to 50%), but is reported in approximately 16.5% of patients, most commonly in patients with macrocephaly and skin manifestations. The optimal frequency of screening MRI is not clear, but it would seem reasonable to recommend every 2 years in macrocephalic patients with associated skin lesions (facial trichelemmomas, papillomatous papules and acral keratoses). The age of onset of these lesions averages 22 years. The primary findings in PHTS include macrocephaly and increased risk for certain types of cancer. The syndrome predisposes to cancers of kidney, breast, thyroid and endometrium.

The most common of the related syndromes is VHL disease with reported incidence of 1:36,000 and prevalence 1:91,000 in Australia (MSAC App 1153 Assessment Report 2011). All other conditions are significantly rarer.

REF Mester J, Eng C. Cowden syndrome: Recognizing and managing a not-so-rare hereditary cancer syndrome. *Journal of surgical oncology*. 2015 Jan;111(1):125-30.

Shuch B, Ricketts CJ, Vocke CD, Komiya T, Middleton LA, Kauffman EC, Merino MJ, Metwalli AR, Dennis P, Linehan WM. Germline *PTEN* mutation Cowden syndrome: an underappreciated form of hereditary kidney cancer. *The Journal of urology*. 2013 Dec;190(6):1990-8.

24. Specify the characteristics of patients with (or suspected of having) the medical condition, who would be eligible for the proposed medical service/technology (including details on how a patient would be investigated, managed and referred within the Australian health care system, in the lead up to being eligible for the service):

Tuberous Sclerosis Complex (TSC):

Tuberous sclerosis is diagnosed based on a clearly defined diagnostic criteria as outlined in the Updated International Tuberous Sclerosis Complex Diagnostic Criteria (2021). Individuals often present in early childhood with infantile spasms, seizures or developmental delay, but may also present in adulthood, typically with characteristic skin lesions, bleeding for renal lesions or other late onset organ specific manifestations. Characteristic clinical features detected in primary care or characteristic imaging features on brain or abdominal imaging would typically result in referral to specialist services (neurology, nephrology, dermatology, ophthalmology, genetics etc.) depending on organ specific manifestations and which point a definitive diagnosis can be made based on clinical criteria or genetic testing.

Patients would only become eligible for MBS funded abdominal MRI after a diagnosis of tuberous sclerosis is established based on the clearly defined diagnostic criteria. At this point patients would undergo a baseline abdominal MRI in line with international consensus guidelines.

Other rare syndromes with increased risk of renal tumors:

The presentation of other rare syndromes associated with the risk of renal tumours will vary across specific conditions. Initial presentation may be based on cutaneous features, symptoms associated with visceral tumours or incidental detection of tumours on investigations performed for other purposes. Following detection of tumours, patients are likely to be referred to specialist surgical or oncological services and atypical features such as multiple tumours or specific histopathological findings may result in referral to a geneticist.

Patients would only become eligible for MBS funded abdominal MRI after a diagnosis is established based either on clinical criteria or as a result of genetic testing.

PART 6b – INFORMATION ABOUT THE INTERVENTION

25. Describe the key components and clinical steps involved in delivering the proposed medical service/technology:

Following the establishment of a diagnosis of tuberous sclerosis complex 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.

26. Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?

N/A

27. If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?

N/A

28. If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e. accessibility, dosage, quantity, duration or frequency)?

The provision of abdominal MRI services including machine eligibility and reporting/accreditation will be subject to rules in the Diagnostic Imaging Services Table (DIST) of the MBS.

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). These legislative requirements will also apply to the proposed MRI item.

29. If applicable, identify any healthcare resources or other medical services that would need to be delivered at the same time as the proposed medical service:

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.

30. If applicable, advise which health professionals will primarily deliver the proposed service:

Radiologist or radiographer. MRI trained personnel are defined within the Australian and New Zealand College of Radiology Safety Guidelines (<https://www.ranzcr.com/Downloads/MRI%20Safety%20Guidelines%20V2.pdf>)

31. If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:

N/A

32. If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:

Nephrologists, metabolic specialists, general physician, clinical geneticist

33. If applicable, advise what type of training or qualifications would be required to perform the proposed service, as well as any accreditation requirements to support service delivery:

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). These legislative requirements will also apply to the proposed abdominal MRI item.

34. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select ALL relevant settings):

Public radiology service

Private radiology service

Inpatient public hospital (admitted patient)

Inpatient private hospital (admitted patient)

(b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:

MRI is available in the radiology departments of most hospitals including some day hospitals, and in some clinics and imaging centres, This application relates to the provision of the MRI service in any of these pre-existing service centres.

35. Is the proposed medical service intended to be entirely rendered in Australia?

Yes

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

36. Nominate the appropriate comparator(s) for the proposed medical service (i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service):

Ultrasound

CT

No imaging because patient can't afford out of pocket costs

37. Does the medical service (that has been nominated as the comparator) have an existing MBS item number(s)?

Yes (please list all relevant MBS item numbers below)
 No

Abdominal Ultrasound 55036

Multiphase abdominal CT scan (MBS items 56401 or 56507);

38. (a) Will the proposed medical service/technology be used in addition to, or instead of, the nominated comparator(s)?

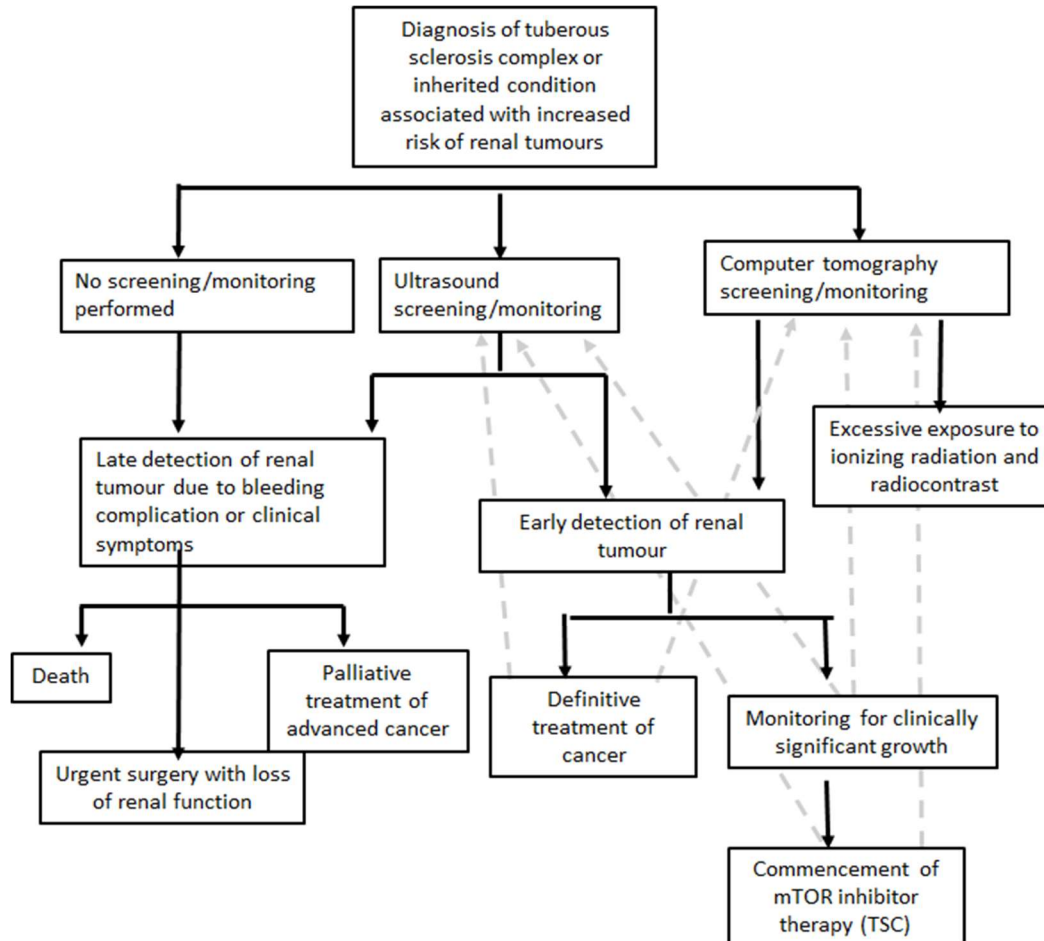
Instead of

(b) If yes, please outline the extent to which the current service/comparator is expected to be substituted

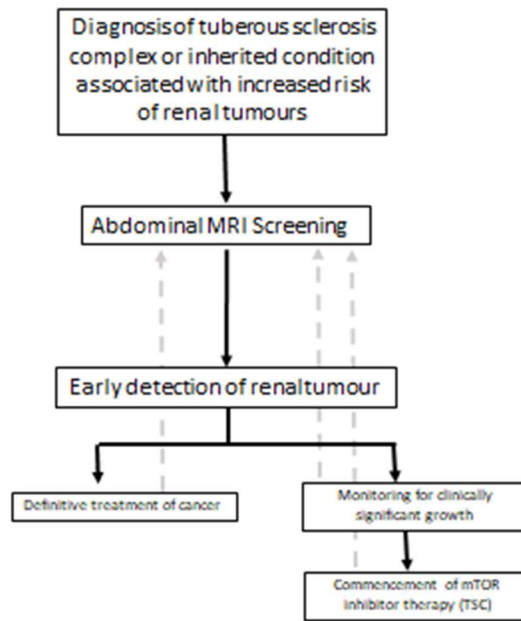
The service will routinely used instead of comparators in line with international guidelines that MRI is clinically superior in diagnosis and management of the TSC and other rare genetic conditions with increased risk of kidney tumours.

PART 6c CONTINUED – INFORMATION ABOUT ALGORITHMS (CLINICAL MANAGEMENT PATHWAYS)

39. Define and summarise the **CURRENT** clinical management pathway (algorithm) that patients follow when they receive the **COMPARATOR** service (i.e. the landscape **before** the proposed service is introduced). An easy-to-follow flowchart is preferred, depicting the current **clinical management pathway**, but dot-points would be acceptable. Please include health care resources used in the current landscape (e.g. pharmaceuticals, diagnostics and investigative services, etc.).



40. Define and summarise the **PROPOSED** clinical management pathway (algorithm) that patients would follow **after** the proposed service/technology is introduced, including variation in health care resources.



PART 6d – INFORMATION ABOUT CLINICAL OUTCOMES

41. Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):

The clinical utility of MRI of the abdomen for the identified population (patients with rare genetic conditions associated with increased risk of kidney tumours) is based on International Treatment Guidelines that have considered evidence of improved accuracy of abdominal MRI when compared with other diagnostic imaging mechanisms such as ultrasound and CT, and reduced exposure to repeated doses of ionizing radiation when compared to CT.

In the case of tuberous sclerosis complex, serial screening with abdominal MRI allows for the early detection of renal angiomyolipomas (AMLs) and the accurate assessment of growth over time. It is recommended that AMLs larger than 3 cm in diameter be treated with an mTOR inhibitor (currently available on the PBS for this indication) to prevent catastrophic and life threatening spontaneous bleeding. The absence of screening will considerably increase the risk of sudden bleeding which may be fatal or require urgent intervention with renal artery embolization or nephrectomy that will result in the loss of renal tissue and chronic kidney impairment and/or kidney failure. Monitoring with an inferior modality such as ultrasound will increase the risk of inadequate treatment and monitoring with CT will increase exposure to ionizing radiation and associated risks of malignancy.

In the case of other inherited conditions at increased risk of renal tumours, early detection of malignant tumours through screening MRI will enable early diagnosis of tumours at a stage when curative surgical intervention is possible and without repeated exposure to ionizing radiation as would be the case with CT base screening programs.

42. Please state what the overall clinical claim is:

Superiority diagnostic test compared to existing funded imaging modalities with decreased adverse effects compared to CT. Overall benefit in mortality through reduction in catastrophic bleeding from AMLs and improved outcomes of malignant tumours through early diagnosis.

43. List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

Health outcomes:

- Decrease mortality rate
- Time to initial diagnosis of tumours
- Time from diagnosis to treatment
- Improved management of treatment
- Reduced exposure to ionizing radiology
- Quality of life scores

Clinical effectiveness outcomes

Accuracy

- Improved sensitivity and specificity compared to existing modalities

Change in management (Therapeutic efficacy)

- Change in treatment pathway: appropriate commencement of mTORi therapy (TSC)
- Avoidance of emergency presentations for spontaneous AML bleeding (TSC)
- Early detection of malignant lesions to facilitate curative surgical management and avoid need for systemic cytotoxic therapy (other inherited conditions)

Safety outcomes (largely covered in previous submission)

- Adverse reaction to contrast agent
- Cumulative effects of multiple contrast agent injections
- Claustrophobia requiring the administration of sedation or general anaesthetic
- Physical harms from follow-up testing
- Other adverse events arising from liver MRI

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

44. Estimate the prevalence and/or incidence of the condition in the proposed population:

TSC has an incidence 1:6,000 and prevalence of 8.8:100, 000 in Australia. (Ref: TSA)
Related conditions: VHL Incidence 1:36,000 and prevalence 1:91,000 in Australia (MSAC App.1153 Assessment Report 2011) or rarer.

45. Estimate the number of times the proposed medical service/technology would be delivered to a patient per year:

For surveillance purposes maximum once per year.

For monitoring treatment efficacy (e.g Everolimus for TSC) one additional MRI performed 3 -6 months after commencement of treatment (one additional scan in lifetime of patient).

46. How many years would the proposed medical service/technology be required for the patient?

Lifetime

47. Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:

700-900 patients

48. Estimate the anticipated uptake of the proposed medical service/technology over the next three years, factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors), as well as provide commentary on risk of 'leakage' to populations not targeted by the service.

Approximately 2200-2700. The risk of leakage is low for this patient population, due to rarity of the conditions proposed under this service, all patients are managed by a small group of specialists. Referral would be made by nephrologists or geneticists and in cases of rural, regional and remote patients, occasionally by a general physician working closely with a nephrology or genetics specialist in a tertiary outpatient clinic.

PART 8 – COST INFORMATION

49. Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:

\$450 for MRI

A claim for the contrast agent will also need to be made in conjunction with this service similar to the items for contrast-enhanced MRI of the liver.

\$120 for contrast agent.

50. Specify how long the proposed medical service/technology typically takes to perform:

45 minutes

51. If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and usage characteristics that defines eligibility for the medical service/technology.

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)

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
Approximately 3- 6 months after disease specific therapeutic intervention is initiated to assess responsiveness (once per lifetime)
Fee: \$450 (MRI) and \$120 (contrast agent)

52. If public funding is sought through an alternative (non-MBS) funding arrangement, please draft a service description to define the population and usage characteristics that defines eligibility for the service/technology.

Not applicable