Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1702 – Abdominal MRI for rare genetic conditions associated with increased risk of renal tumours

Applicant: **Rare Voices Australia**

Date of MSAC consideration: **30-31 March 2023**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of abdominal magnetic resonance imaging (MRI) for (i) annual surveillance to detect newly developed renal tumours, or (ii) assessment of changes over time to the renal tumour, in patients with rare inherited conditions associated with an increased risk of renal tumours, was received from Rare Voices Australia by the Department of Health and Aged Care.

2. MSAC's advice to the minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported the creation of new Medicare Benefits Schedule (MBS) items for abdominal magnetic resonance imaging (MRI), using intravenous (IV) contrast when appropriate, for annual surveillance to detect newly developed renal tumours and monitor existing renal tumours in patients with rare heritable genetic conditions with an increased lifetime risk of renal tumours.

MSAC noted that – in addition to MRI being an accurate technique for detecting, characterising and monitoring renal tumours – it was safer for this patient population than computed tomography (CT) because of the lack of ionising radiation and therefore lower associated cancer risk. MSAC considered that this safety benefit was an important consideration for ensuring readily available access to MRI for this population with high clinical need, given their requirement for serial imaging from a young age. While noting the limitations of the economic evaluation, MSAC considered that abdominal MRI was likely cost-effective compared with CT based on the safety outcome of radiation-induced cancer avoided. MSAC also noted that abdominal MRI is recommended in national and international guidelines for this patient population. MSAC considered that the financial cost to the MBS would be modest and acceptable.

The MSAC supported MBS items and explanatory note are provided below:

Annual surveillance item (PICO set 1)

Category 5 – Diagnostic Imaging Services

Item XXXX

MRI – scan of the abdomen, requested by a specialist or consultant physician, to assess the development and/or growth of renal tumours in patients with a confirmed clinical and/or molecular diagnosis of a genetic disorder associated with an increased risk of developing renal tumours.

For any particular patient – applicable not more than once in a 12 month period.

Restricted to one scan per 12 months.

(R) (Anaes) (Contrast)

Fee: $637.25

Tumour monitoring item (PICO set 2)

Category 5 – Diagnostic Imaging Services

Item YYYY

MRI – scan of the abdomen, requested by a specialist or consultant physician, to assess a patient with a known renal tumour who has:

a) a confirmed clinical and/or molecular diagnosis of a genetic disorder associated with an 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 XXXX; 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)

Fee: $637.25

Proposed explanatory note to accompany items XXXX and YYYY

For Items XXXX and YYYY, access to these items is for patients with a confirmed clinical and/or molecular diagnosis of a rare genetic disorder associated with a >N% risk* of developing renal tumours. Examples of such disorders could include:

- 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 an increased risk of developing renal tumours.

* N% risk will be determined through consultation with clinical experts before the proposed items are implemented

Consumer summary

This is an application from Rare Voices Australia requesting Medicare Benefits Schedule (MBS) listing of abdominal magnetic resonance imaging (MRI) for rare genetic conditions associated with increased risk of renal tumours. Renal tumours are abnormal growths in the kidney which may include but are not restricted to cancers.

There are several genetic (inherited) conditions that can increase a person's risk of developing renal tumours. People with these conditions are managed by a specialist and need to have regular scans of their belly (abdomen) to see whether any tumours have developed in their kidneys. The types of available scans can include ultrasound, computed tomography (CT) or MRI. The kinds of renal tumours which it is important to detect in this group of patients are those which are potentially lethal, which include cancers as well as other types of renal tumours which are not cancerous but can lead to major health problems and cause death due to bleeding. Ultrasound and CT are funded under the MBS for scanning these conditions, but not currently MRI. If a renal tumour is identified, these people may be treated early, and/or are then regularly scanned to track the tumour's size and see if it needs any additional treatment, and to assess for additional renal tumour development.

All three types of scans are effective at finding and tracking renal tumours. The main difference between them is that CT exposes the person to very low levels of radiation, but MRI and ultrasound do not. Being exposed to radiation can increase a person's risk of developing cancer, separate to the risk from the underlying condition. This is an especially important consideration for people who need to have regular scans, because they may repeatedly be exposed to radiation, which increases their risk of developing cancer more than the risk from the very low level of radiation from a single CT scan.

MSAC considered that MRI was just as effective as ultrasound and CT, and was safer than CT for patients with these conditions. Expert guidelines also recommend using MRI for these patients. Listing MRI on the MBS for these conditions would allow clinicians to provide guideline-based care and choose the most appropriate type of scan for their patient. MSAC also thought that MRI was good value for money.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC supported MBS listing of abdominal MRI for rare genetic conditions associated with increased risk of renal tumours, because it is safe, effective and good value for money.

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

MSAC noted that the application sought Medicare Benefits Schedule (MBS) listing of abdominal magnetic resonance imaging (MRI), using intravenous (IV) contrast where appropriate, for rare genetic conditions associated with increased risk of renal tumours. The item would be used for annual surveillance to detect newly developed renal tumours, as well as serial scanning of previously identified renal tumours to assess significant change.

MSAC noted that genetic testing for a number of heritable kidney diseases is already available on the MBS and once these genetic abnormalities are detected patients undergo serial imaging assessment aiming for early detection of tumours. MSAC noted that the rationale for this practice is that such early detection improves treatment options and response and hence increases patient utility (mainly longevity) and this is supported by real world data. Recently MSAC approved a conceptually similar application, namely whole body MRI for a specific genetic abnormality that increases the risk of malignancy at multiple sites, which became available on the MBS on 1 March 2023 (MSAC Application 1668). MSAC noted that current practice for screening using imaging is highly variable, and typically involves a combination of ultrasound (US), computed tomography (CT) and MRI.

MSAC noted that the application uses tuberous sclerosis complex (TSC) and Von Hippel–Lindau disease (VHL) as exemplars (as these are the most common of the conditions), but that at least nine other genetic conditions would also be eligible. MSAC noted that there were a wide range of tumours associated with these conditions, many of which carry a mortality risk but not all of which are malignant. For TSC, 80% of individuals are at risk of developing angiomyolipomas (AML) which appear from around age 18 and tend to grow rapidly. For VHL there is increased risk of multiple benign and malignant tumours at multiple sites.

The combined list of genetic abnormalities account for 4% of all renal tumours, the remainder are not associated with known heritable risk. Other genetic conditions are likely to be identified in the future that would also meet the conditions for the proposed population and are encompassed by the proposed item descriptor.

MSAC noted the two populations specified in the PICO:

- PICO set 1 (population 1): surveillance of patients with confirmed clinical or molecular diagnosis of a condition that results in a high risk of developing renal tumours
- PICO set 2 (population 2): patients diagnosed with a syndrome associated with increased risk of kidney cancer who require monitoring 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.

MSAC confirmed that the comparators under current surveillance imaging protocols of US and CT (with and without contrast) were appropriate.

MSAC considered that the MBS item descriptors proposed, and the associated fees, were appropriate. MSAC advised that the list of eligible conditions should be included in an explanatory note rather than the item descriptor itself, to allow the list to be revised over time more easily. MSAC noted that the N% risk in the explanatory note will be determined through consultation with clinical experts before the proposed items are implemented.

On the evidence base for effectiveness, MSAC noted that 23 studies and two systematic reviews met the inclusion criteria for PICO set 1 looking at the accuracy of MRI against CT or US. For PICO set 2, only 2 studies met the inclusion criteria for assessing accuracy of abdominal MRI against CT. No studies were identified that compared abdominal MRI with US. No studies met the inclusion criteria for assessing management change resulting from abdominal MRI compared with abdominal CT or US. MSAC noted that the original literature searches identified five studies that did not meet the inclusion criteria because they did not report results according to the imaging modality used but provided information on the effectiveness of treatments for the exemplar populations: TSC-associated AML or renal cell carcinoma (RCC) and VHL-associated RCC.

MSAC noted that the evaluation also reported on the results of a literature search, limited to studies published in the last 10 years to identify additional studies, and 11 studies were included from this search. However, as studies reporting on surgical and ablative outcomes were still underrepresented, two additional studies published since 2000 were also included.

MSAC noted that there were no direct comparative studies relating to safety in this patient cohort, so safety was assessed using general safety data available for MRI, CT and US. US is the safest imaging modality. CT and MRI have similar safety implications relating to the use of contrast agents, but the main difference is that CT exposes patients to ionising radiation, which increases the lifetime risk of radiation-induced cancer. Although modelling of cancer risk from very low level radiation exposure from diagnostic imaging is difficult and controversial, an increased risk is likely to be present in this group of patients who may have screening from a young age and for many years. MSAC therefore considered that MRI has a superior safety profile compared with CT.

MSAC noted the evidence relating to clinical effectiveness and confirmed that MRI is generally non-inferior compared with CT, but in some circumstances may be superior (such as for lesion characterisation e.g. fat poor AMLs). MSAC considered that the rare nature of these conditions means that high level evidence is unlikely to be generated to resolve these uncertainties, and that consensus guidelines (including EviQ guidelines and international guidelines) recommend MRI for detection and monitoring of renal tumours in these conditions. MSAC noted that listing MRI on the MBS for these conditions would allow clinicians to provide guideline-based care and choose the most appropriate imaging modality for their patient. MSAC considered that it was highly unlikely that MRI would replace US, but it was likely that MRI would replace CT.

MSAC noted the economic evaluation presented a cost-effectiveness analysis (CEA) with the ICER generated as the incremental cost per cancer avoided. MSAC noted that the model could have been extended as per Kang et al (2014) to account for HRQoL to generate QALYs and a cost utility analysis (CUA) could have been undertaken to generate an incremental cost per QALY gain, however this had not been undertaken. MSAC noted that the meaning of an ICER generated as the incremental cost per cancer avoided used in this context was not comparable to ICERs typically considered by MSAC which are generated from CUAs (whenever the data allowed) in the form of an incremental cost per QALY gained. The CEA undertaken which generated an incremental cost per cancer case avoided led to the need to interpret what a 'case of cancer avoided' means as 'cancer avoided' can be interpreted to refer to either the benefit to the patient experience of avoiding cancer, or the benefit of avoiding cancer in its totality including avoiding the resource costs of hospitalisation for the cancer. MSAC noted that under the first interpretation (which only accounts for patient experience) the ICER is $61,888 per cancer avoided but under the second interpretation of avoiding cancer in its totality the ICER is $108,234 per cancer avoided. MSAC considered that a reported ICER of $108,234 per cancer avoided (where this is interpreted as capturing the value of averting cancer in its totality) was cost effective which also meant by implication that a reported ICER of $61,888 per cancer avoided (which accounted for only the benefit to patient experience) would also be cost-effective. For transparency, this Public Summary Document has been updated to reflect the reported ICER of $108,234 per cancer avoided (where this is interpreted as capturing the value of averting cancer in its totality) as the ICER upon which MSAC has based its advice.

MSAC noted that other limitations of the economic evaluation were that:

- the estimation of the number of cancer cases avoided was unnecessarily simplistic and did not account for differences in age and sex at the time of radiation exposure, which can be significant.
- the model starts at age 20, but MSAC noted that surveillance starts at an earlier age as recommended in expert consensus guidelines. The pre-MSAC response acknowledged that lowering the age would have a significant impact on radiosensitivity and therefore a larger impact on cancers avoided by switching to MRI. MSAC considered that the number of cancer cases avoided in the economic evaluation is therefore an underestimate, but is reasonable in the absence of any international benchmark.
- The cost of cancer estimated was assumed to be a one-off excess healthcare cost and did not account for differentiations in costs between phase of cancer care or cancer type.

Overall, while noting the limitations of the economic evaluation (partly to the limited clinical trial data), MSAC considered that abdominal MRI was likely cost-effective compared with CT based on the safety outcome of radiation-induced cancer avoided.

MSAC considered that as the number of individuals in the target population is too small for high level evidence to be obtained regarding the "best" surveillance methods this imposed a major limitation on the accuracy of any economic modelling.

MSAC noted the financial and budgetary impacts, and considered that the overall cost to the MBS would be modest (about $250,000 each year). MSAC also noted that, in paediatric

populations, MRI is often done under general anaesthetic and can be used to scan multiple areas of the body at once, which may result in cost savings.

MSAC noted that people in the target population live with the ongoing potential for the development of tumours, which can be distressing for them and their relatives, and considered that there was a value of knowing from imaging that may be able to identify a lack of new tumour development, or tumour stability. MSAC noted that given the rarity of these conditions in the target population, it is unlikely that more robust evidence will be developed for the effectiveness of abdominal MRI surveillance in this population. MSAC considered therefore that these patients should be able to have access to the MRI surveillance requested in this application as this is recommended by experts in the field in consensus guidelines such as the EviQ Guidelines, noting that there are currently no limitations on CT or US use.

MSAC noted that implementing this item may raise issues relating to equity of access to MRI for people in regional and remote areas. Patients may also experience out-of-pocket costs for MRI, but the gap for patients was unclear.

Other discussion

MSAC recognised its preference for economic evaluations to be presented as CUAs (whenever the data allowed) rather than CEAs, as stated in the MSAC Guidelines, in order to avoid having to undertake complex interpretations of the ICER, such as in this case. However, MSAC also recognised that CEA is highly informative in relevant circumstances.

4. Background

MSAC has not previously considered abdominal MRI for (i) annual surveillance to detect newly developed renal tumours, or (ii) assessment of changes over time to the renal tumour in patients with rare inherited conditions associated with an increased risk of renal tumours.

5. Prerequisites to implementation of any funding advice

MRI is a well-established diagnostic and monitoring tool used for many conditions.

6. Proposal for public funding

The proposed intervention is MRI of the abdomen using gadolinium-based contrast (where applicable) performed in 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, for the purpose of surveillance (to detect new tumours or changes in known tumours) in patients belonging to PICO Set 1, and to determine treatment response or tumour size in patients belonging to PICO Set 2. Abdominal MRI is expected to replace abdominal CT in these patients.

The clinical claim made by the applicants is that the use of abdominal MRI is:

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

Contrast-enhanced (CE)-MRI is commonly performed in Australian clinical practice. Images in corticomedullary phase, nephrographic phase and/or excretory phase are obtained using either a 1.5 T or 3 T machine. Image acquisition sequences often used include:

- T1 or T2-weighted gradient or spin echo
- T1-weighted gradient or spin echo with contrast
- T1- or T2 weighted with fat-suppression
- T2-weighted respiratory-gated turbo spin echo (TSE).

PICO Set 1

The proposed item descriptor for public funding for abdominal MRI to be used for 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, with amendments suggested by PASC, is presented in Table 1.

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 MRI of other parts of the body.

Of note, was that the exclusive use of MRI is not unanimously recommended for this patient group. In patients with VHL and *BAP1* tumour pre-disposition syndrome, the eviQ guidelines specify that abdominal MRI should be done two yearly with US done in the intervening year. In BDH syndrome, the eviQ guidelines recommend either three yearly MRI or two-yearly US if there are no abnormalities. This is discussed below (Table 3).

Table 1 Proposed MBS item descriptor for PICO set 1

Category 5 – Diagnostic Imaging Services
MBS item XXX MRI – scan of the abdomen, requested by a specialist or consultant physician, 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:** $637.25 **Benefit:** 75% = $477.95 85% = $549.35

PICO Set 2

The target population for PICO set 2 are patients diagnosed with a syndrome associated with increased risk of kidney cancer who require monitoring 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. In this population, abdominal MRI should 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.

However, this is not reflected in the wording of the proposed item number. The wording in bold italics has been added to reflect that a few patients may need additional imaging between annual surveillance MRI (Table 2).

Table 2 Proposed MBS item descriptor for PICO set 2

Category 5 – Diagnostic Imaging Services
MBS item YYY MRI – scan of the abdomen, requested by a specialist or consultant physician, ***to assess a patient with a known renal tumour who has***: a) 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 XXX; 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:** $637.25 **Benefit:** 75% = $477.95 85% = $549.35

As discussed in PASC, the applicant agreed the fee should be aligned with existing MBS items for abdominal MRI to reflect current costs of this service. MBS item 63473 is $627.20 for an MRI of the pelvis and upper abdomen.

To be consistent with most other MBS-listed MRI items, the item descriptors should specify that the service must be requested by a specialist or consultant physician.

The 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 Royal Australian and New Zealand College of Radiologists (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.

PASC suggested as an alternative to listing all eligible conditions in the item descriptors that the wording could be '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

As contrast would be used for most scans, except those where it is contraindicated, e.g. estimated glomerular filtration rate (eGFR)<30ml/min/1.73m^2; non-compatible medical device in situ; metallic foreign body in situ, etc. As discussed in PASC, the applicant agreed following PASC that the existing MBS item for the use of gadolinium-based contrast in conjunction with an MRI service (MBS Item 63491, schedule fee $45.50) should be used for this application.

7. Population

The proposed 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 hereditary 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);
- 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).

However, more genetic conditions may be identified in the future that would also meet the conditions for the proposed population.

Because of the diversity of these conditions, the assessment has taken an exemplar approach in line with recommendations in the ratified PICO Confirmation. The two most common genetic conditions associated with renal tumours were selected as exemplars for assessment: TSC and VHL. These conditions are described below and the rationale for their selection as exemplars is discussed.

Tuberous Sclerosis Complex

TSC is an autosomal dominant genetic disease caused by pathogenic variants in the tumour suppressor genes, Tuberous Sclerosis Complex 1 (*TSC1)* and Tuberous Sclerosis Complex 2 (*TSC2)*. Pathogenic variants in either gene result in inactive proteins that cannot inhibit the mammalian target of rapamycin (mTOR) pathway. This leads to relatively uncontrolled cell growth leading to development of benign tumours (hamartomas) in multiple organs, such as the brain, kidneys, skin, heart, lungs and bones. As TSC manifests across multiple organs, a number of specialties can be involved in the diagnosis and management of patients (e.g. neurologists, dermatologists).

Renal involvement is potentially serious and common in TSC. Renal AMLs and cysts are the two characteristic renal lesions of TSC. Approximately 70–90% of patients with TSC have renal AMLs

and 30% have cysts. RCC may also occur in TSC. It has been estimated that the incidence of RCC in TSC is 2–4% and occur in patients at a younger age than sporadic RCC.

The role of kidney imaging in patients with TSC is to identify and characterize renal lesions, both benign and malignant, and detect any potential complications.

Von Hippel Lindau

VHL disease is an autosomal dominant, multisystem tumour syndrome that results from a variety of germline variants in the von Hippel Lindau (*VHL*) tumour suppressor gene on chromosome 3p25–26. The VHL protein interacts with various hypoxia-inducible transcription factors (HIFs) to encourage their degradation. These proteins are hypoxia responsive and are upregulated in hypoxia and become transcription factors for various growth factors. Pathogenic variants of the *VHL* gene produce disrupted VHL proteins that allows HIF to accumulate. This leads to increased expression of growth factors that have important roles with respect to tumour formation and growth.

VHL syndrome occurs with a frequency of approximately 1:36,000 and is the most common hereditary renal tumour syndrome. The mean age of onset of VHL disease is 26 years and there is 90% penetrance by age 60 years. VHL is characterised by both benign and malignant tumours in specific organs of the body, including the central nervous system (CNS), eye, inner ear, kidney, pancreas, adrenal gland, and epididymis in the male and broad ligament in the female.

Renal involvement is characterised by the development of clear cell RCCs in up to 70% of patients and renal cysts in 20–60% of patients. VHL-related RCCs occur at a mean age of 40 years and are of typically of low nuclear grade (1–2 out of 4), slow growing, and are usually bilateral and multifocal.

Metastatic RCC is responsible for up to 50% of deaths in patients with VHL. However, similar to those with other inherited renal tumour syndromes, treatment should be a balance between removing the tumour and preserving enough renal parenchyma to maintain renal function. Many of these patients will have multiple tumours during their lifetime. The repeated surgical treatments of new RCCs in these patients will eventually result in chronic kidney disease. This results in a higher incidence of cardiovascular events and death, with a median overall survival in these patients of around 50 years.

The "3-cm rule"

The surveillance of large numbers of patients with VHL has resulted in a broad consensus on how RCC in these patients should be managed and has led to the "3-cm rule", where small (< 3 cm) RCCs detected by imaging should be managed by active surveillance and then nephron-sparing surgery or ablative techniques performed when the solid lesion reaches 3 cm in diameter[1].

However, the "3-cm rule" is not absolute. Both tumour size and the growth kinetics determine the risk of metastatic disease, and both of these parameters should guide the decision on when to excise RCCs. The "3-cm rule" should be considered to be a point at which to balance the risk of metastasis with the potential morbidities of multiple procedures. If the "3-cm rule" is followed, the expected disease progression-free survival rate for patients with VHL-associated RCC was 76% at 5 years and 20% at 8 years.

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[1] Carrion D, et al. (2020). Invasive management of renal cell carcinoma in von Hippel-Lindau disease. *Cent European J Urol,* 73(2): 167-172.

Maher, E. (2018). Hereditary renal cell carcinoma syndromes: diagnosis, surveillance and management. *World J Urol,* 36(12): 1891-1898.

PICO Set 1

The "3 cm rule" approach to the management of RCCs has been extrapolated to include patients with TSC, Birt–Hogg–Dube syndrome and other hereditary renal tumour syndromes with slow growing RCCs. However, the "3 cm rule" is not suitable for patients with hereditary leiomyomatosis and renal cell carcinoma (HLRCC) and other hereditary renal tumour syndromes with fast-growing RCC, which can metastasise early and are not reliably detected by renal ultrasound (US).

The surveillance and treatment recommendations for individual syndromes is described in Table 3. In current Australian clinical practice, surveillance is most likely to carried out using US and CT. It is likely that proposed monitoring using abdominal MRI will replace the use of CT. However, as US is inexpensive and widely available, it is unlikely to replace US. If confirmatory imaging is required following US, the test would most likely be MRI instead of CT.

Table 3 Surveillance / treatment initiation recommendations for inherited renal tumour syndromes

Disease / genes affected / function	Type and frequency of renal tumour	Surveillance / treatment initiation recommendations
Non-RCC tumours		
Tuberous Sclerosis Complex (TSC) *TSC1, TSC2* Activation of the mTOR pathway Only 30% of TSC is inherited	70–90% of patients with TSC develop one or more AMLs	MRI or low dose CT is recommended at least every 1–3 years throughout the lifetime of the patient from age 12, to monitor growth of AMLs First-line therapy for AMLs measuring > 3 cm, treatment with an mTOR inhibitor is recommended. Treatment by transarterial embolisation of AML >4cm is primarily focused on the avoidance of acute haemorrhage. Recurrence rate is high.
RCC syndromes where the 3cm rule applies		
Von Hippel Lindau (VHL) *VHL* Activation of hypoxic response pathways	Up to 70% of patients with VHL develop clear cell RCC	Biannual abdominal MRI with abdominal US in intervening years from age 10 (EviQ: VHL – risk management) Intervention should occur when a lesion reaches 3 cm: the origin of the 3 cm rule
Tuberous Sclerosis Complex (TSC) *TSC1, TSC2* Activation of the mTOR pathway	1–4% of patients develop RCC of various histological types	MRI or low dose CT is recommended at least every 1–3 years throughout the lifetime of the patient from age 12, to provide early detection of renal tumours The "3-cm rule" applies
Birt Hogg Dubè (BHD) *FLCN* Activation of the mTOR pathway	30% of affected patients have RCC of various histological type. They are of intermediate aggressiveness, but some can be aggressive	Baseline MRI at age 20 years Patients without a renal tumour should have an MRI every 3 years The interval for those with renal tumours <3 cm is dependent on location and growth rate. The "3-cm rule" applies
Hereditary Papillary Renal Cancer (HPRC) *MET* Activation of MET signalling pathway	HPRC produces papillary type 1 tumours, with as many as 3400 microscopic tumours per kidney, in all patients	Baseline abdominal MRI at age 30 years. Patients without a renal tumour should have an MRI every 3 years The interval for those with renal tumours <3 cm is dependent on location and growth rate The "3-cm rule" applies
Microphthalmia-associated transcription factor *MiTF*	Increased risk of papillary type 1 renal tumours	No recommendations for screening. Annual screening for those in whom renal tumours are detected

Disease / genes affected / function	Type and frequency of renal tumour	Surveillance / treatment initiation recommendations
Activation of MAPK signalling pathway		
RCC syndromes where the 3cm rule may not apply		
Hereditary Leiomyoma Renal Cell Carcinoma (HLRCC) *FH* Activation of hypoxic response pathways Epigenetic changes	15–32% of patients with an *FH* pathogenic variant develop papillary type II renal tumours	Annual MRI for patients from age 18 years. Surgical resection (with wide margin, or complete nephrectomy) if RCC detected HLRCC tumours are aggressive and are treated as soon as they are diagnosed
Hereditary paraganglioma/ pheochromocytoma syndrome (HPPS) *SDHA, SDHB, SDHC, SDHD* Activation of hypoxic response pathways Epigenetic changes	The risk of a renal cancer is 10–15% by age 70 for *SDHB*. Only slightly increased for other 3 genes. Tumours can exhibit aggressive behaviour and one third of patients developed metastatic disease	*SDHA*: abdominal MRI once every 5 years from age 18 *SDHB*: 2-yearly abdominal MRI from age 10 *SDHC/D*: abdominal MRI once every 4 years from age 18 Tumours should be treated expeditiously after diagnosis
Translocation of chromosome 3 (involving *VHL, PBRM1, BAP1*, and/or *SETD2*) Activation of hypoxic response pathways	Up to 70% of patients develop clear cell RCC	Annual surveillance is not necessary unless there is a history of renal cancer. When lesions are found they should be treated
Lynch Syndrome (LS) *MLH1, MSH2, MSH6, PMS2, EPCAM* Activation of the mismatch DNA repair pathway	2–5% of patients develop upper urothelial malignancies 1% develop renal cell adenocarcinomas	Annual urinalysis with cytology to detect microscopic haematuria is recommended. No recommendations for routine imaging If there are any sign of haematuria, CT Urography is the preferred imaging modality, but MR urography can be helpful
Renal Medullary Cancer (RMC) in association with sickle cell trait *HBB* Leads to tissue hypoxia and a secondary erythrocytosis	RMC is a highly aggressive type of renal cancer but is very uncommon	No recommendations for surveillance Once a tumour is discovered it should be treated as soon as possible
PTEN hamartoma tumour syndrome (PHTS) *PTEN* Activation of phosphoinositide 3-kinase (PI3K) signalling pathway	The lifetime risk of RCC is estimated to be 5-35%. Cancers are papillary or chromophobe in nature	2-yearly abdominal MRI or US starting at age 40 2-yearly US The French Cowden Disease Network proposed to begin screening at 30 years Annual imaging if family history of renal cancer Treatment decisions must balance the risk of metastatic RCC with maintenance of kidney function
BAP1 tumour pre-disposition syndrome *BAP1* Altered chromatin architecture, DNA damage response and cell cycle regulation	9–13% of patients develop clear cell carcinoma	Annual imaging with alliterating MRI and US from age 30 years (EviQ: BAP1 – risk management) Treatment decisions must balance the risk of metastatic RCC with maintenance of kidney function

Disease / genes affected / function	Type and frequency of renal tumour	Surveillance / treatment initiation recommendations
Familial non-syndromic Renal Cancer (FRC) No identified genetic cause Likely to be multigene inheritance	Tumours are typically clear cell carcinomas	No specific recommendations Treatment decisions must balance the risk of metastatic RCC with maintenance of kidney function

Source: Table 19 in DCAR
AML = angiomyolipoma; CT = computed tomography; DNA = deoxyribonucleic acid; HLRCC = hereditary leiomyoma renal cell carcinoma; MRI = magnetic resonance imaging; mTOR = mammalian target of rapamycin; RCC = renal cell carcinoma; RMC = renal medullary cancer; US = ultrasound

PICO Set 2

The target population for PICO set 2 are patients diagnosed with a syndrome associated with increased risk of kidney cancer who require monitoring for the purposes of evaluating changes in clinical condition or suspected complications of known renal tumours arising between their annual surveillance MRI, or to assess the effect of a new disease specific therapeutic intervention.

Given that up to 80% of patients with TSC experience AML, it may be reasonable to expect that a large proportion of patients accessing MRI for assessment of treatment response, will be those receiving treatment for TSC-related AML. For patients with TSC, treatment response assessment would be expected three to six months after initiation of mTOR inhibitor therapy (everolimus).

For patients with other hereditary renal tumour syndromes, 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 invasive ablative procedures and partial or radical nephrectomy.

In current Australian clinical practice, RCC response to treatment is more likely to be monitored by CT rather than MRI. Thus, MRI is likely to replace CT to monitor treatment effectiveness in RCC.

It is unclear if US is currently used to monitor the response to treatment in Australian clinical practice. It may be used to monitor the response of AMLs to mTOR inhibitors. However, it is uncertain if abdominal MRI would replace US for this application. It is also uncertain if abdominal MRI would be required as an additional test. No evidence on the use of MRI compared to US to monitor treatment response was identified in the literature search to answer this question.

8. Comparators

Computed tomography

In Australian clinical practice, multiphase abdominal contrast-enhanced CT (CECT) scans are associated with the MBS items 56407 and 56507. Multiphasic CECT imaging is usually performed in three phases (unenhanced, arterial/corticomedullary phase, and nephrogenic phase with or without the excretory phase). However, some institutions may only do the unenhanced and nephrogenic phases, as the arterial/corticomedullary phase is only required for treatment planning. Image acquisition using CT is faster than for MRI.

Radiation exposure is still a concern with CT, although the radiation dose has reduced drastically over the years with helical scanners and iterative reconstruction. The nephrogenic phase is often doubled up as a full CT abdomen and pelvis which would increase slices/dose, while the

nephrogenic and excretory phases can be combined and imaged at the same time with a dual bolus technique.

Ultrasound

Abdominal US is associated with MBS item 55036. US is an inexpensive and safe methodology that is readily accessible and suitable for initial imaging of the kidneys, especially in children, to determine the presence of any cystic or solid lesions.

Although US was considered to be a comparator in the PICO Confirmation ratified by PASC, MBS funding of abdominal MRI is very unlikely to affect the current use of US. But where confirmatory imaging is required the test would most likely be MRI instead of CT.

9. Summary of public consultation input

Consultation input was received from five [5] professional organisations, three [3] consumer organisations and ten [10] individuals, all care givers. The eight [8] organisations that submitted input were:

- Australian and New Zealand Society of Nephrology (ANZSN)
- Australian Society of Medical Imaging and Radiation (ASMIRT)
- 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)
- Genetic Alliance Australia (GAA)

All feedback received was supportive of public funding for the service.

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 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.
- The USANZ considered that inclusion of additional relevant syndromes should be clarified (e. g. hereditary papillary type 1 RCC, SDH-srRCC), and also include coverage for additional new conditions with an increased risk of renal cancers that may be identified in the future. It also noted that urologists 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 MRI with their regular brain MRI.

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 US; serial monitoring of growth is more accurate on cross sectional MRI imaging; and cumulative radiation dose from recurrent computed 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 MRI 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 MRI with brain MRI where patients require sedation for their MRI.

The feedback considered that public funding of abdominal MRI 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 MRI.

10. Characteristics of the evidence base

A total of 23 studies and two systematic reviews met the inclusion criteria for assessing the test accuracy of abdominal MRI in detection of malignant renal lesions compared to CT or US in PICO Set 1. Two studies met the inclusion criteria for assessing the accuracy of abdominal MRI in evaluating treatment response compared to CT as the reference standard in PICO Set 2. No studies were identified that compared abdominal MRI with US in PICO Set 2.

No studies met the inclusion criteria for assessing the change in management resulting from abdominal MRI compared with abdominal CT or US.

The original literature searches identified five studies that did not meet the inclusion criteria because they did not report results according to the imaging modality used but provided information on the effectiveness of treatments for the exemplar populations: TSC-associated AML or RCC and VHL-associated RCC.

A quick literature search, limited to studies published in the last 10 years, was conducted to identify additional studies. and 11 studies were included. However, studies reporting on surgical and ablative outcomes were underrepresented, so two additional studies published since 2000 were also included.

No comparative evidence for safety was identified; safety is discussed further in section 9 below.

Table 4 presents a summary of the included evidence.

Table 4 Key features of the included evidence for PICO Set 1 and PICO Set 2

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base
Accuracy and performance of the test (cross-sectional accuracy)	2 systematic reviews and 23 NHMRC level II to III-2 diagnostic accuracy studies for PICO Set 1 2 small NHMRC level III-1 diagnostic accuracy studies for PICO Set 2	PICO Set 1 ☒ k=2 SRs n=3,360 ☒ k=23 n=1,722 PICO Set 2 ☒ k=2 n=21	AMSTAR-2 (k=2 SRs) Low risk of bias QUADAS-C (k=18) QUADAS-2 (k=7) Overall most studies had a low risk of bias
Prognostic evidence (longitudinal accuracy)	No studies were identified in the literature search	☐ k=0 n=0	NA
Change in patient management	No studies that met the inclusion criteria were identified in the literature search	☐ k=0 n=0	NA
Health outcomes	No studies that met the inclusion criteria were identified in the literature search Eighteen studies were identified from other sources that provide information of treatment effectiveness	☒ k=18 n=10.163	Not done as studies did not meet inclusion criteria
Safety	No comparative safety information was identified in the literature search. Information was sourced from authoritative information websites and clinical guidelines, and an additional, non-systematic literature search identified 6 observational studies that provided information	☒ k=6 n=1,843,963	Not done as studies did not meet inclusion criteria

AMSTAR = a measurement tool to assess systematic reviews; k=number of studies, n=number of patients; NHMRC = National Health and Medical Research Council; PICO = population, intervention, comparator, outcomes; QUADAS-2 = quality assessment of diagnostic accuracy studies tool for comparison of an index test with a reference standard; QUADAS-C = quality assessment of diagnostic accuracy studies tool for comparison of 2 or more tests with a reference standard; SR = systematic review

11. Comparative safety

Safety of MRI compared to CT and US

As there were no comparative safety studies that met the inclusion criteria, general safety information related to the three imaging modalities (MRI, CT and US) including information from

authoritative information websites and clinical guidelines, and the results of an additional, non-systematic literature search were considered instead.

All three types of imaging are undertaken widely in Australia and the safety profile for them is generally accepted, with individual clinicians responsible for assessing the risk-benefit ratio for their patient's circumstances. The main safety concern with CT is the exposure to ionising radiation. MRI and CT can both be undertaken without contrast enhancement; in this case, the side effects of MRI are minimal, but the radiation dose received in CT is doubled when the same scan is undertaken both with and without contrast. US does not use ionising radiation (similar to MRI) and is a safe procedure and poses no risk to the patient.

There are risks associated with the use of the contrast agents used for both MRI and CT, although the risk is low (in particular with MRI). However, both are associated with higher risks in patients with renal function impairment.

Gadolinium-containing contrast media are associated with a very rare condition called nephrogenic systemic fibrosis (NSF), that can occur in people with chronic or severe renal disease. There is no treatment for NSF and it may contribute to patient death.

Patients with kidney disease are at greater risk of harm from iodine-containing contrast used for CT. The contrast media can temporarily worsen kidney function in patients with existing severely impaired kidney function. Occasionally, the damage can be prolonged and may require treatment with dialysis.

As people with hereditary renal tumour syndromes, such as TSC and VHL, are more likely to have renal disease than the general population, these particular safety concerns are of relevance to the population of interest. However, it is standard practice for all patients at risk of kidney disease who are undergoing CT or MRI to have their kidney function assessed by their clinician prior to receiving contrast.

12. Comparative effectiveness

PICO Set 1

Diagnostic accuracy of MRI, CT and US in detecting RCC compared to the histopathology reference standard.

Five studies compared the ability of MRI and CT to detect RCC in patients with renal lesions and three studies compared the ability of MRI and CT to detect any malignant tumour type (68–82% being RCCs) in patients with renal lesions. These studies used mostly CE-MRI with T1 and T2-weighted imaging sequences and CE dynamic or multidetector CT. Five studies investigated the ability of DW-MRI to distinguish between RCC and benign tumours using ADC values. The 2x2 data or receiver operating characteristic (ROC) analysis data were extracted from these studies and the sensitivity and specificity calculated. The median (range) sensitivity and specificity values were calculated and are presented in Table 5.

A systematic review (SR) comparing the diagnostic accuracy of MRI, CT and US compared to a histopathology reference standard was identified in the literature search. The individual studies included in the SR were mostly single modality studies, where the patients were only imaged once with MRI, CT or US. This differs from the individual studies included in the report, which compared the accuracy of MRI and CT (and in one case also US), to the histopathology reference standard. The SR calculated the median sensitivity and specificity values for MRI, CT and US in detecting RCC in patients with renal lesions compared to histological examination. The median (range) sensitivity and specificity values for of CE-MRI and CECT were calculated from the data provided by the SR. The median (range) results are summarised in Table 5.

Table 5 Median sensitivity and specificity of MRI, CT and US in detecting RCC and/or other malignant lesions compared to a histopathology reference standard

Comparison	Imaging mode	Sensitivity: median (range)	Specificity: median (range)
SR by Vogel et al. (2019)*:	MRI (all)	87.5% (65–100), k=8	89% (33–100), k=8
Single modality studies:	CE-MRI	85% (65–100), k=5	91.5% (65–100), k=5
RCC vs benign:	CT (all)	88% (67–98), k=14	75% (25–100), k=14
	CECT	88% (67–98), k=10	74% (47–100), k=10
	US	56% (46–60), k=3	71% (12–73), k=3
Comparative studies:	DW-MRI	91.7% (71–100), k=5	83.3% (78.1–100), k=5
RCC vs benign:	CE-MRI	88.9% (71.4–100), k=5	73.9% (46.7–90.9), k=3
	CECT	92.6% (35.7–100), k=5	68.4% (63.6–75.8), k=3
	US	88.9%, k=1	NA
Comparative studies:	CE-MRI	91.2% (77.0–100), k=3	66.8% (62.5–70.0), k=3
Malignant vs benign:	CECT	87.9% (75.7–100), k=3	68.5% (62.5–73.3), k=3

* Vogel, C, Ziegelmuller, B, Ljungberg, B, Bensalah, K, Bex, A, Canfield, S, Giles, RH, Hora, M, Kuczyk, MA, Merseburger, AS, Powles, T, Albiges, L, Stewart, F, Volpe, A, Graser, A, Schlemmer, M, Yuan, C, Lam, T & Staehler, M 2019, 'Imaging in Suspected Renal-Cell Carcinoma: Systematic Review', Clinical Genitourinary Cancer, vol. 17, no. 2, 2019, pp. e345-e355.
CE = contrast enhanced; CT = computed tomography; DW = diffusion weighted; k = number of studies; MRI = magnetic resonance imaging; NA = not available; RCC = renal cell carcinoma; US = ultrasound

As the individual studies included in the report compared the accuracy of at least two imaging modalities with respect to the reference standard, reducing the risk of selection bias. In contrast the studies included in the SR mostly compared only one imaging modality to the reference standard, increasing the risk of selection bias. Hence, the median (and range) sensitivity and specificity values calculated from the comparative studies were used in exploratory scenario analysis in the economic model.

Overall, all imaging modalities were very sensitive in distinguishing RCC or any malignant lesion from benign renal lesions compared to the reference standard; varying from 89% to 93%. However, DW-MRI was more specific in distinguishing RCC from benign renal lesions at 83%, compared with CE-MRI and CECT (74% and 68%, respectively).

Staging of renal lesions using MRI, CT and US compared to a histopathology reference standard

Two studies provided 2x2 data to determine the accuracy of MRI and CT in staging RCC as T1 vs T2 or greater. The median sensitivity and specificity of MRI and CT compared to histopathology did not differ greatly, and the ranges almost completely overlapped. One study provided data to determine the sensitivity and specificity of US in staging RCC compared to the reference standard.

This suggests that MRI and CT are equivalent in their ability to distinguish stage T1 RCC from stage T2 or greater. US also appears to be equivalent to MRI and CT in distinguishing stage T1 RCC from stage T2 or greater as the sensitivity and specificity values for US fell within the range of values determined for both CT and MRI.

Three studies reported on the ability of MRI and CT compared to a histopathology reference standard to accurately stage renal cysts as malignant or benign according to the Bosniak Classification System. All three studies provided 2x2 data so that the accuracy of MRI and CT compared to a histopathology reference standard in distinguishing malignant cysts (Bosniak ≥3) from benign cysts (Bosniak ≤2F) could be determined.

Five studies provided sufficient data for 2x2 tables to determine the accuracy of MRI and CT compared to a clinical reference standard in detecting an inferior vena cava (IVC) thrombus versus no thrombus. Both MRI and CT were highly sensitive and fairly specific with a median sensitivity of 100% and a median specificity of 87%. One study reported that US was able to

detect the thrombus in 88% of cases. As the study only included patients diagnosed with RCC with IVC thrombus, the specificity could not be determined. The results are summarised in Table 6.

Table 6 Median sensitivity and specificity of accurately staging renal lesions using MRI, CT and US compared to a histopathology reference standard

Comparison	Imaging mode	Sensitivity: median (range)	Specificity: median (range)
T1 versus T2-T4 staging of RCC	CE-MRI CECT US	90.6% (89.0–99.5), k=2 87.5% (85.9–97.5), k=2 96.0%, k=1	83.3% (66.7–91.9), k=2 77.8% (72.7–89.1), k=2 84.2%, k=1
Bosniak ≤2F vs ≥3 staging of renal cysts	CE-MRI CECT	90% (71–100), k=3 81% (36–100), k=3	66% (40–91), k-3 64% (50–76), k=3
Staging of IVC thrombus compared with no thrombus in RCC	CE-MRI CECT US	100% (25.0–100), k=5 100% (25.0–100), k=5 88%, k=1	86.8% (0–100), k=4 87.3% (0–100), k=4 NA

CE = contrast enhanced; CT = computed tomography; k = number of studies; MRI = magnetic resonance imaging; NA = not available; RCC = renal cell carcinoma; US = ultrasound

Overall, both CE-MRI and CECT are very accurate at detecting IVC thrombus involvement in RCC. CE-MRI, CECT and US all appear to be equally useful in differentiating RCC between stage T1 and stage T2 or higher. Approximately 10% are wrongly classed as T1 and 20% are wrongly classified as stage 2 or higher. The single study reporting on the accuracy of US found little difference in the sensitivities and specificities calculated for all three modalities. However, both CE-MRI and CECT were less able to reliably distinguish between benign and malignant cysts according to the Bosniak classification scale. Approximately 10% (by CE-MRI) and 20% (by CECT) were determined to be benign (Bosniak 2F or lower) and later found to be malignant on continued surveillance. Conversely, approximately 35% were thought to be malignant (Bosniak 3 or higher) and found to be benign by histopathology after surgical intervention.

Diagnostic challenges in differentiating RCC from various benign lesions

Imaging by either CE-MRI and CECT present difficulties in distinguishing RCCs, without ambiguity, from certain types of benign growths, which include complex cysts, oncocytomas and AMLs.

AMLs

Distinguishing RCC from fat-poor AMLs is an important issue in the clinical management of patients with TSC. As these patients are predisposed to renal failure, avoidance of unnecessary surgical removal of benign fat-poor AMLs is essential.

To date, no imaging sequence has been identified that can reliably distinguish RCC and fat-poor AMLs. Even follow-up imaging may be problematic. One study found that out of three indeterminate masses that showed rapid growth (>0.5 cm/year) as determined by regular follow-up with repeat CT or MRI, only one was diagnosed as RCC by histopathology. The other two renal masses were diagnosed as fat-poor AMLs.

The combined results from one SR and two individual studies indicate that the most sensitive imaging sequence for the distinguishing RCC from fat-poor AML was DW-MRI. Using DW-MRI, 12–16% fewer patients with RCC would be misdiagnosed as having a benign tumour than with using either T2-based MRI sequences or CT. Conversely, T2-based MRI sequences and CT would result in 5–8% fewer patients with benign lesions being misdiagnosed and receiving unnecessary surgery than with DW-MRI.

Oncocytomas

Distinguishing RCC from oncocytomas is important in patients with Birt-Hogg-Dubé syndrome who may present with bilateral, multicentric oncocytomas. Oncocytomas may also be present in patients with TSC or SDH–associated paraganglioma/pheochromocytoma.

As no radiologically robust means of discriminating RCCs from oncocytomas has yet been identified, the majority of oncocytoma are diagnosed after the surgical removal. Obtaining a differential clinical diagnosis is complicated by renal mass biopsy (RMB) not being definitive because up to 20% of RCCs have oncocytic features, and the mean growth rate of oncocytomas are equivalent to that of RCCs.

Out of 110 benign lesions included in the three studies investigating the diagnostic accuracy of MRI and CT in detecting malignant versus benign tumours, 15 were oncocytomas. All 15 were misdiagnosed as RCC by both CECT and CE-MRI. This suggests that the routine sequences for both CT and MRI, with or without enhancement, are not able to differentiate between RCC and oncocytomas. One study found that both CE-MRI and DW-MRI were not able to correctly identify the six oncocytomas included, however, when DW-MRI sequences were added to CE-MRI findings, three out of the six oncocytomas were correctly classified as benign.

Complex renal cysts

Distinguishing RCC from complex renal cysts is important in patients with VHL or TSC. Approximately 30% of patients with VHL and 14–32% of patients with TSC may present with renal cysts. Patients with TSC may also have polycystic kidney disease as deletions affecting the *TSC* genes may also affect the adjacent *PKD1* gene, which is responsible for polycystic kidney disease.

Up to 8% of renal cysts do not meet the strict criteria for a simple cyst or a cystic neoplasm and are considered indeterminate, and approximately 10% of RCCs initially appear as a simple or complex cyst. Therefore, identifying complex and multifocal cystic renal lesions that need either surgical intervention or continuous surveillance represents a major challenge.

The Bosniak Classification System for renal cysts (using CT or MRI) is the most common tool used in clinical practice to predict the likelihood of malignancy. The biggest difficulty lies in distinguishing between a class IIF and a class III cyst. This report concluded above that approximately 35% of patients with Bosniak III cysts, actually had a benign cyst and received unnecessary surgery. One study concluded that CE-MRI may better characterize complex, cystic lesions in the kidney compared to CECT as it was able to reliably define an enhancing nodule within a cystic renal lesion.

Tumour sizing and growth rates

Accurately determining tumour size via radiographic imaging is an important factor in clinical TNM staging of RCC. One study found that smaller (0–2 cm) tumours were found to be significantly smaller in size and larger (>7 cm) tumours were significantly larger in size on pathology compared to MRI, CT and US. The difference in tumour size determined by imaging versus pathology led to a change in TNM staging (per size criteria) in 16%, 25% and 16% of cases for MRI, CT and US, respectively. Among all three modalities, 3–7% of all tumours were upstaged after surgical resection, whereas downstaging after surgical resection occurred in 13%, 18% and 11% of cases for MRI, CT and US, respectively.

The growth rate of renal tumours can be very important in treating patients with hereditary renal tumour syndromes if the 3 cm rule applies, as in patients with VHL. Once a potentially malignant renal mass has been identified by imaging, it is important to determine if the tumour requires treatment or further imaging before the next annual or biannual scheduled surveillance occurs.

One study using DW-MRI found that VHL-related RCC tumours with lower baseline ADC values tend to have faster growth rates than tumours with higher ADC values, and that smaller tumours and tumours with lower ADC values tend to have a shorter doubling time.

Change in management

No evidence was identified for change of management associated with use of MRI (either with or without contrast) in comparison to CT and/or US that met the inclusion criteria. Therefore, the impact of MRI over CT or US on the clinical management of patients with TSC or VHL is uncertain.

As the diagnostic accuracy of MRI was noninferior to CT, only a small number of patients would be expected to have a change in diagnosis with respect to RCC or AML at risk of causing complications. Thus, few patients would be expected to have a change in management with the proposed introduction of MRI.

Treatment effectiveness

When renal tumours are correctly identified and characterised, they may be appropriately treated. The clinical claim suggested that MRI was more accurate at detecting and characterising tumours than CT or US, so it was expected that MRI would result in earlier treatment in some patients. The safety and effectiveness of treatments for AMLs and RCCs was therefore evaluated, to determine if earlier treatment would result in superior health outcomes. However, given the uncertainty regarding any incremental difference in the accuracy of MRI over CT or US, or any documented alteration in the management of patients on the basis of MRI rather than CT or US, the last step of the linked evidence approach does not contribute to the conclusions, and has therefore not been presented.

PICO Set 2

Effectiveness of MRI and CT in measuring the treatment response in RCC patients

Two very small studies provided data comparing the effectiveness of CE-MRI and CECT in measuring the response to ablative treatment in patients with RCC.

One study found that CE-MRI had an advantage over CECT in monitoring response to ablation procedures as CE-MRI subtraction images are better able to confirm non-enhancement of the inflammation tissue and reactive oedema; the presence of residual or recurrent tumours would be detected by tumour enhancement.

The second study found a strong association between DCE parameters that are dependent on the tumour tissue permeability and perfusion and the percentage change in tumour volume from the 12-month CT scan onwards. The authors hypothesised that patients who experienced tumour growth after ablative therapy still had viable tumour vasculature while patients whose tumours reduced in size likely did not.

The small volume of evidence on the use of MRI for monitoring changes to renal tumours over time was considered insufficient to make any conclusions on the comparative effectiveness of one imaging modality compared over another.

Clinical claim

Given the absence of any clear difference in the accuracy of MRI compared to CT at imaging AMLs and RCCs, and the absence of any literature demonstrating a difference in clinical management subsequent to MRI versus CT or US, the evidence suggests that the use of abdominal MRI results in noninferior effectiveness compared with abdominal CT. The evidence

was insufficient to make any conclusions on the comparison between MRI and US. The clinical claim of superior effectiveness of MRI was therefore not met.

However, the information considered from authoritative websites and clinical guidelines, and evidence from five studies found in an additional, non-systematic literature search supported the claim of superior safety of abdominal MRI compared with abdominal CT.

While the applicant's pre-ESC response argued that expert clinical consensus guidelines agree that MRI is superior to other forms of surveillance for this population, the rejoinder noted that assessment of the accuracy of diagnostic technologies is always based on the evidence of test performance reported in the literature and not on consensus guidelines as consensus guidelines are based on expert opinion rather than on a thorough analysis of the data.

13. Economic evaluation

Based on the interpretation of the clinical evidence given in Section 2, the use of abdominal MRI results in noninferior effectiveness and superior safety compared with abdominal CT for PICO set 1 (annual surveillance). The claim of superior safety was made on the basis that CT imaging exposes patients to ionising radiation which can lead to excess cancer based on a dose-response relationship. There was insufficient evidence to make conclusions on the comparative effectiveness of one imaging modality over another for monitoring changes to renal tumours over time.

A cost-effectiveness analysis estimating the incremental cost per radiation induced cancer avoided was originally presented for proposed use of abdominal MRI versus CT scan for the periodic surveillance, with the interpretation of 'case of cancer avoided' restricted to the benefit of the patient experience in calculating the ICER. The analysis was subsequently revised to broaden the interpretation of 'case of cancer avoided' to include the benefit of avoiding cancer in its totality including avoiding the resource use costs of hospitalisation for the cancer, as was recommended by ESC and subsequently supported by MSAC in considering its advice. The recommended screening frequency for TSC is 1-3 years and for VHL is every 2 years[2]. Therefore, the base case evaluation assumes that the target population has two-yearly imaging. The economic evaluation takes the form of decision tree analysis followed by a Markov cohort simulation transitioning between the two-health states (alive and dead) over a time horizon of 50 years, and a 1-year cycle length. Costs and outcomes are discounted at 5% per annum. The individuals entering the model are first divided into separate pathways based on the surveillance options available; MRI or CT scan. Radiation induced cancer risk associated with CT scans is then added into the model based on the cumulative number of CT scans performed.

An exploratory scenario analysis integrates notional estimates of sensitivity and specificity for MRI and CT scanning and based on the test outcomes, further costs associated with confirmatory testing and treatment.

No comparative evidence was found related to the proposed use of abdominal MRI versus CT scan for the assessment of response to treatment or tumour growth three to six months post initiation of treatment (PICO set 2). Hence, no economic analysis is presented for this listing.

A summary of the key components of the economic evaluation is presented in Table 7.

[2] EviQ guidelines: URL:https://www.eviq.org.au/ (accessed 25 October 2022) and National Comprehensive Cancer Network (NCCN) panel recommendations (Motzer, R 2020, 'NCCN Guidelines Insights: Kidney Cancer, Version 1.2021', *J Natl Compr Canc Netw*, 18(9): 1160-1170.

Table 7 Summary of the economic evaluation for proposed use of abdominal MRI versus CT scan for the periodic surveillance

Component	Description
Perspective	Australian health care system
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.
Prior testing	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); periodic surveillance.
Comparator	Computed tomography (CT) with or without contrast agent
Type(s) of analysis	Cost-effectiveness analysis
Outcomes	Radiation induced cancers avoided (interpreted as the benefit of avoiding cancer in its totality including avoiding the resource costs of hospitalisation for the cancer)
Time horizon	50 years in the modelled base case
Computational method	Markov model
Generation of the base case	Modelled stepped economic evaluation: Step 1: Cost comparison of direct imaging costs only Step 2: Cost effectiveness analysis (Healthcare system perspective) - Estimates the ICER by calculating the ratio of incremental direct imaging costs to incremental cancers developed Scenario analysis: Step 2 + inclusion of notional differential imaging accuracy and confirmatory testing to differentiate between malignant and benign RCCs and treatment.
Health states	Alive (with regular surveillance) and dead
Cycle length	1 year
Transition probabilities	All analyses: • Excess cancer risk associated with cumulative radiation exposure • Disease specific background mortality Used in scenario analysis • Diagnostic accuracy (sensitivity and specificity of the imaging modality • Incidence of RCC in target population (lifetime risk converted to annual probability)
Discount rate	5% for both costs and outcomes
Software	TreeAge Pro 2022 and Microsoft Excel 2019

CT = computed tomography; MRI = magnetic resonance imaging; RCC = renal cell carcinoma

[1] Given the absence of any clear difference in the accuracy of MRI compared to CT at imaging AMLs and RCCs, and the absence of any literature demonstrating a difference in clinical management subsequent to MRI versus CT or US, the evidence suggests that the use of abdominal MRI results in noninferior effectiveness compared with abdominal CT. However, abdominal MRI results in superior safety compared with abdominal CT. Therefore, the base case analysis assumes equivalent clinical effectiveness (that is both MRI and CT have 100% sensitivity and 100% specificity) and only a safety difference is modelled.

Note table updated based on MSAC's advice

A summary of the sources of data used in the economic analysis is presented in Table 8.

Table 8 Summary of the inputs used in the economic evaluation

Parameter	Reference	Source
Transition probabilities		
Excess cancer risk associated with the cumulative radiation exposure	Calculated using formula: age-specific background cancer × (IRR – 1).	Calculated using the IRR for exposed versus unexposed Australian patients reported by Mathews (2013)[1].which included abdominal CT. The IRR (1.24) and increment per scan (0.16) reported over mean follow-up of 9.5 years were annualised (annualised IRR and increment per scan estimated as 1.0285 and 0.018 respectively). The background cancer risk is based on AIHW (2022) [2] data.
Disease specific mortality risk	SMR×background mortality	Age-specific background mortality risk from Life tables ABS; average of SMRs reported in Eijkemans (2015) and Peng (2021) [3]
Used in scenario analysis only		
Sensitivity and specificity of imaging test	Table 5	Section 12.
Lifetime risk[a] of renal cancer associated with the syndrome	Birt-Hogg-Dubé syndrome: 25% Hereditary leiomyomatosis and RCC: 24% Tuberous Sclerosis Complex: 3% Von Hippel- Lindau: 50% Tuberous Sclerosis Complex related angiomyolipoma: 80%	Published literature and Table 3
Costs		
Costs associated with surveillance	Cost per MRI scan of $678.20 comprising MRI cost of $637.25 and contrast agent cost of $45.50 (for 90% of services); cost per CT scan of $481	Proposed fee for abdominal MRI comprising MBS item 63473 (fee updated July 2022) and MBS item 63491 (fee updated July 2022); weighted fee for MBS items 56407 and 56507 for CT– scan of upper abdomen and pelvis
Used in scenario analysis only		
Cost of surgical removal of renal tumours	$21,844.15	Weighted average cost of AR-DRGs L03B and L03C[5]
Annual cost of treating benign tumours with mTOR inhibitors	$21,148.71	PBS item 2985D for everolimus 10 mg tablet (pack of 30 with DPMQ $1,737.06)
Cost of confirmatory testing	Cost associated with biopsy and histopathology of the sample of $1255.90 comprising: Initiation of a patient episode -outpatient ($8.20); Renal biopsy, under image guidance ($182.35); Guidance imaging ($115.75);	Estimated using following MBS items and day hospital admission: - MBS item 73926 - MBS item 36561 - MBS item 55036 - MBS item 72846 - MBS item 72813 - Tier 2 1003 (IHPA 2022a) - MBS item 20862 - MBS item 23035

Parameter	Reference	Source
	Immunohistochemical examination of biopsy material ($59.60); Light microscopy ($71.50); Theatre and other surgical costs (4-6 hours hospital stay ($609)); Initiation of management of anaesthesia, renal procedures ($146.65); Time units, 3 basic units (30-45 min) ($62.85)	

ABS = Australian Bureau of Statistics; AIHW = Australian Institute of Health and Welfare; AR-DRGs = Australian Defined diagnosis-related groups; CT = computed tomography; DPMQ = dispensed price for maximum quantity; IRR = incidence rate ratio; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; SMR = standardised mortality ratio

[1] Mathews, JD, Forsythe, AV, Brady, Z, Butler, MW, Goergen, SK, Byrnes, GB, Giles, GG, Wallace, AB, Anderson, PR, Guiver, TA, McGale, P, Cain, TM, Dowty, JG, Bickerstaffe, AC & Darby, SC 2013, 'Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians', Bmj, vol. 346, May 21, p. f2360.

[2] AIHW 2022, *Table S1b.1: Cancer incidence by 10-year age groups (00–09, 10–19, …, 80–89, 90+), by sex, actual data from 1982 to 2018 with projections to 2022, Cancer Data in Australia*, Australian Institute of Health and Welfare, Canberra.

[3] ABS 2021, *Table 1.9 Life Tables, Australia, 2018–2020, Catalog no. 3302055001DO001_20182020 Life Tables, 2018-2020,*; Eijkemans, MJC 2015, 'Long-term Follow-up Assessing Renal Angiomyolipoma Treatment Patterns, Morbidity, and Mortality: An Observational Study in Tuberous Sclerosis Complex Patients in the Netherlands', *American Journal of Kidney Diseases*, vol. 66, no. 4, 2015/10/01/, pp. 638-645, Peng, JH, Tu, HP & Hong, CH 2021, 'A population-based study to estimate survival and standardized mortality of tuberous sclerosis complex (TSC) in Taiwan', *Orphanet J Rare Dis*, vol. 16, no. 1, Aug 3, p. 335.

[4] Goldsbury, DE, Yap, S, Weber, MF, Veerman, L, Rankin, N, Banks, E, Canfell, K & O'Connell, DL 2018, 'Health services costs for cancer care in Australia: Estimates from the 45 and Up Study', *PLoS One*, vol. 13, no. 7, p. e0201552.

[5] AR-DRGs L03B and L03C (surgical DRG codes for kidney, ureter and major bladder interventions for neoplasm; intermediate and minor Complexities, respectively); IHPA 2022b, *Table 3 Cost Weights for AR-DRG Version 10.0, Round 24 (2019-20), National Hospital Cost Data Collection, Public Sector Cost Report*.

[a] Lifetime risks reported in the literature converted to biennial probabilities using probability to rate to probability conversion formulas. Lifetime risk is assumed between 20 to 70 years, that is over 50 years. Formula used are: r = -ln(1-p)/t and p = 1-exp(-rt); where r is the rate of event, p is the probability and t is the time period

Note table updated based on MSAC's advice

A stepped approach is used to generate the base case analysis in order to incorporate the translations of the clinical evidence and other key model assumptions separately to distinguish the effect of each of these on the results. CECT is associated with exposure to ionising radiation that can cause cancer. While the model captures the number of excess cancers due to radiation exposure, detailed and final health outcomes related to these are not included in the model. It is assumed that the average rate of surveillance is one imaging scan every 24 months in the modelled population across both intervention and comparator arms; in practice, this may vary based on the patient medical history, symptom presentation and compliance to recommendations.

The modelled results with the final ICER outcome of 'radiation induced cancer avoided' are presented in a stepped manner in Table 9. The stepped analysis results in a final ICER outcome of $108,234 per radiation-induced cancer avoided.

Table 9 Stepped economic evaluation (undiscounted and discounted costs and outcomes)

Stepped analysis	MRI	CT	Increment
Step 1: Cost comparison of direct imaging costs only			
(Biannual imaging in people with hereditary syndromes with predisposition to RCC, and includes cost associated with imaging over the 50-year modelled time horizon (undiscounted). Outcome presented is cost comparison.			
Undiscounted Results Total direct cost difference over 50 years.	$14,814	$10,497	$4,317
Discounted Results Total direct cost difference over 50 years.	$6,261	$4,436	$1,824
Step 2 Cost effectiveness analysis (Healthcare system perspective)			
Estimates the ICER by modelling excess cancer risk associated with CT radiation to identify the number of cancer cases associated with CT over the 50-year time horizon and calculating the ratio of incremental direct imaging costs to incremental cancers developed			
Undiscounted imaging costs Undiscounted radiation-induced cancers	$14,814 0.000	$10,497 0.0971	$4,317 –0.0971
Undiscounted Result: ICER, per radiation induced cancer avoided			MRI is more costly and more effective than CT $44,458 per cancer case avoided
Discounted imaging costs Discounted radiation-induced cancers*	$6,261 0.00	$4,436 0.0169	$1,824 –0.0169
Discounted Result: ICER per radiation induced cancer avoided.			$108,234 per cancer case avoided

CT = computed tomography; ICER = incremental cost effectiveness ratio; MRI = magnetic resonance imaging; RCC = renal cell carcinoma

*Discounting of radiation-induced cancer events is an abstract conceptualisation; The discounting factor can be applied to either the event rate or the cost, but not both.

Note: Discounting applied to costs and outcome at 5%p.a.

Note table updated based on MSAC's advice

The base case result (discounted) indicates that compared with CT, proposed abdominal MRI costs an additional $1,824 and results in 1.7% radiation induced cancers avoided. This results in an incremental cost effectiveness ratio (ICER) of $108,234 per radiation induced cancer avoided.

The results are not influenced by the disease specific risk of renal cancers (AMLs or RCCs), diagnostic accuracy of tests, or treatment costs associated with disease specific risk of renal cancers as the inputs in these analyses are test costs, and risk and costs associated with cancers due to exposure to ionising radiation. Scenario analysis was conducted integrating median values for sensitivity and specificity for CT and MRI and treatment costs (using VHL as an exemplar) into the base case model. This analysis is exploratory because these values are notional; the data is associated with wide and overlapping confidence intervals and comes from disparate sources, such that the clinical assessment considered the diagnostic effectiveness of each as similar. Health outcomes associated with diagnosis, surveillance, treatment delay or over treatment are not captured in the model, but cost implications of additional testing and management are included. Key assumptions in the scenario analyses are:

- Patients with true RCCs (disease positive) will have nephron sparing surgery irrespective of the test results (both true positive and false negative).
- Patients who are disease negative but test positive (false positive, benign renal tumours) are assumed to be managed as indeterminate results and incur cost associated with confirmatory testing (biopsy and histopathology of the sample).

- Due to ongoing routine monitoring, detection of interval cancers in false negative patients will not be delayed long enough to impact final outcomes - i.e. they will ultimately be diagnosed and receive effective treatment.

Due to lack of evidence, it was not possible to quantify the impact of delayed treatment and the assumption of no detrimental health effect is conservative.

The results of the scenario analysis estimated that, when including notional sensitivity and specificity, MRI was associated with a reduced incremental cost of $72,036 per radiation induced cancer avoided. This analysis adds the additional short-term costs associated with correctly or incorrectly identifying RCCs and short-term management (these costs would 'cancel out' in the base case where accuracy is assumed equivalent). Table 10 presents the results (discounted) for the scenario analyses.

Table10 Scenario analysis integrating test accuracy for MRI and CT using VHL as an exemplar

	Δcost	**Δradiation-induced cancers**	**Incremental cost per radiation induced cancer avoided**
Median values for sensitivity and specificity for MRI (89%, 74%) and CT (93%, 68%)	$1,214.28	0.0169	$72,036
Lower value (71%) for MRI sensitivity	$1,244.24	0.0169	$73,813
Higher value (100%) for MRI sensitivity	$1,195.28	0.0169	$70,909
Lower value (46.7%) for MRI specificity	$4,281.44	0.0169	$253,992
Higher value (90.9%) for MRI specificity	–$702.70	0.0169	ICER in SE-quadrant; MRI dominates CT
Lower value (35.7%) for CT sensitivity	$1,145.26	0.0169	$67,941
Higher value (100%) for CT sensitivity	$1,223.26	0.0169	$72,568
Lower value (63.6%) for CT specificity	$673.02	0.0169	$39,926
Higher value (75.8%) for CT specificity	$2,048.73	0.0169	$121,539

Δ = difference in cost or outcome for MRI compared with CT; CT = computed tomography; ICER = incremental cost effectiveness ratio; MRI = magnetic resonance imaging; RCC = renal cell carcinoma; SE = south-east; VHL = von Hippel-Lindau
Note table updated based on MSAC's advice

Univariate sensitivity analyses were conducted around key parameters for the cost-effectiveness analysis. The analyses were most sensitive to the cost of MRI and increment in cancer incidence rate ratio (IRR) (exposed vs unexposed) per CT scan. The analysis was not sensitive to the screening interval or baseline IRR used in the model.

Table 11 Key drivers of the model

Description	Method/Value	Impact Base case: $108,234/radiation induced cancer avoided
Increment in cancer IRR (exposed versus unexposed)	Estimates for cancer IRR and increment in IRR per scan were based on a retrospective analysis of Australian Medicare records (Mathews et al. 2013). The study found that over a mean follow-up of 9.5 years, overall cancer incidence was 24% (CI 95% 20%, 29%) greater for exposed than for unexposed people, and the IRR increased by 0.16 (95% CI, 0.13 to 0.19) (annually; 0.0185 (95% CI, 0.0146, 0.0219) for each additional CT scan.	*This estimate is uncertain, therefore upper and lower confidence bounds of the estimate were tested. Increasing the increment in IRR per scan to 0.0219, decreased the ICER by 16%, whereas decreasing this estimate to 0.0146, increased the ICER by 22%. The ICER is highly sensitive to changes in this estimate*
Modelled time horizon	Time horizon of 50 years was chosen in the modelled base-case to capture the impact of lifelong surveillance in the proposed population.	*The ICER is highly sensitive to the time horizon. When shorter time horizon is used ICER increases significantly. The excess cancer risk and costs are higher towards the later years due to increase in the cumulative dose of CT scan, and these may not be captured with the shorter time horizon.*

CI = confidence interval; CT = computed tomography; ICER = incremental cost effectiveness ratio; IRR = incidence rate ratio; MRI = magnetic resonance imaging; RCC = renal cell carcinoma
Note table updated based on MSAC's advice

Table 12 presents results for key univariate sensitivity analyses.

Table 12 Results of the key sensitivity analyses

	∆cost	∆radiation-induced cancers	ICER	% change
Base case	$1,824	0.0169	$108,234	-
Increment in IRR of cancer per scan - (base case: 1.82%)				
Increment: 1.46%	$1,824.45	0.0138	$131,885	21.85%
Increment: 2.19%	$1,824.45	0.0200	$91,324	–15.62%
Time horizon (base case: 50 years)				
20 years	$1,302.17	0.0021	$620,609	473.40%
30 years	$1,588.00	0.0056	$285,096	163.41%
40 years	$1,746.76	0.0111	$157,949	45.93%
Discounting rate (base case: 5% per annum)				
0%	$4,317.11	0.0971	$44,458	–58.92%
3.50%	$2,255.72	0.0276	$81,836	–24.39%

∆ = difference in cost or outcome for MRI compared with CT; CT = computed tomography; ICER = incremental cost effectiveness ratio; IRR = incidence rate ratio; MRI = magnetic resonance imaging; RCC = renal cell carcinoma; SE = South-East
Note table updated based on MSAC's advice

The analyses were most sensitive to the increment in cancer incidence rate ratio (IRR) (exposed vs unexposed) per CT scan, discounting rate applied to costs and outcomes and modelled time horizon.

14. Financial/budgetary impacts

Note: The financial impact analysis presented in the DCAR reflects the Greatest Permissible Gap (GPG) that applied until 31 October 2022 ($87.90). The GPG increased to $93.20 on 1 November 2022. The increase does not impact the total cost of MBS services, however results

in an approximate increase of $5.30 per service funded by patient gap payments, and an equivalent reduction in cost to the MBS. This change resulted in a <2% decrease in the estimated net financial impact to the MBS (as explored in a sensitivity analysis presented in the Table 16).

Periodic surveillance using ultrasound (US) and computed tomography (CT) with/without contrast is a current clinical practice in persons with rare genetic syndromes with a predisposition to benign/malignant renal tumours. However, these services either are performed in the public hospitals or are claimed using general MBS items for CT and US services. In the absence of current usage data for the comparator services, an epidemiological approach is used to estimate the financial implications of funding proposed MRI services.

Table 13 summarises the estimated costs associated with the listing of proposed MRI services for annual surveillance and treatment monitoring. Proposed abdominal MRI will cost approximately $522,000 annually to the MBS by the sixth year of MBS listing.

Table 13 Estimated costs associated with the listing of proposed services

	2023	2024	2025	2026	2027	2028
Proposed MRI service in PICO set 1						
Estimated number of MRI services for surveillance *(A)*	765	775	785	795	804	813
Cost to MBS (B + C)	*$447,073*	*$452,916*	*$458,706*	*$464,242*	*$469,506*	*$474,875*
MRI *(B = A × $549.35)* [2]	$420,450	$425,945	$431,391	$436,597	$441,547	$446,596
Contrast *(C = A × $38.65 × 90%)*[2]	$26,623	$26,971	$27,316	$27,645	$27,959	$28,279
Copayment (D + E)	*$71,994*	*$72,934*	*$73,867*	*$74,758*	*$75,606*	*$76,470*
MRI *(D = A × $87.90)* [2]	$67,275	$68,154	$69,026	$69,859	$70,651	$71,459
Contrast *(E = A × $6.85 × 90%)*[2]	$4,718	$4,780	$4,841	$4,900	$4,955	$5,012
Proposed MRI service in PICO set 2						
Estimated number of MRI services for monitoring *(F= A × 10%)* [1]	77	78	79	79	80	81
Cost to MBS (G+ H)	*$44,707*	*$45,292*	*$45,871*	*$46,424*	*$46,951*	*$47,487*
MRI *(G = F × $549.35)* [2]	$42,045	$42,595	$43,139	$43,660	$44,155	$44,660
Contrast *(H = F × $38.65 × 90%)*[2]	$2,662	$2,697	$2,732	$2,765	$2,796	$2,828
Copayment (I + J)	*$7,199*	*$7,293*	*$7,387*	*$7,476*	*$7,561*	*$7,647*
MRI *(I = F × $87.90)* [2]	$6,728	$6,815	$6,903	$6,986	$7,065	$7,146
Contrast *(J = F × $6.85 × 90%)*[2]	$472	$478	$484	$490	$496	$501
Total cost to MBS	**$491,780**	**$498,208**	**$504,577**	**$510,666**	**$516,457**	**$522,362**
Total copayment	$79,193	$80,228	$81,254	$82,234	$83,167	$84,118

CT = computed tomography; MBS = Medicare Benefits Schedule; MRI = magnetic resonance imaging

[1] For patients requiring MRI for the assessment of treatment response, there is a general sparseness of evidence across all of the kidney cancer syndromes. It was assumed that 10% of the persons undergoing surveillance imaging will have treatment monitoring.

[2] Source: PICO; proposed fee for the MRI service $637.25 (85% rebate: $549.35 and copayment $87.90) (note: the greatest permissible gap of $87.90 is applied to this item), Scheduled fee for contrast use, MBS item 63491, is $45.50 (85% rebate: $38.65 and copayment: $6.85). It is assumed only 90% of the services will use contrast agent due to contraindications.

The net financial implications to the MBS resulting from the proposed listing of abdominal MRI are summarised in Table 14.

Table 14 Net financial implications of abdominal MRI to the MBS

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated use and cost of the proposed health technology						
Number of people eligible for MRI	2,122	2,150	2,177	2,204	2,229	2,254
Number of people who receive MRI	842	853	864	874	884	894
PICO set 1 (for surveillance)	*765*	*775*	*785*	*795*	*804*	*813*
PICO set 2 (for treatment monitoring)[1]	*77*	*78*	*79*	*79*	*80*	*81*
Number of services of MRI with contrast agent	758	768	777	787	796	805
Cost to the MBS (copayments excluded)	$491,780	$498,208	$504,577	$510,666	$516,457	$522,362
Change in use and cost of other health technologies						
Change in use of CT scan [2]	–584	–591	–599	–606	–613	–620
Surveillance	*–531*	*–537*	*–544*	*–551*	*–557*	*–564*
Treatment monitoring [1]	*–53*	*–54*	*–54*	*–55*	*–56*	*–56*
Change in use of ultrasound	0	0	0	0	0	0
Net change in costs to the MBS (copayments excluded)	$238,359	$241,474	$244,561	$247,513	$250,319	$253,181
Net financial impact to the MBS	**$253,421**	**$256,734**	**$260,016**	**$263,154**	**$266,138**	**$269,181**

CT = computed tomography; MBS = Medicare Benefits Schedule; MRI = magnetic resonance imaging
[1] For patients requiring MRI for the assessment of treatment response, there is a general sparseness of evidence across all of the kidney cancer syndromes. It was assumed that 10% of the persons undergoing surveillance imaging will have treatment monitoring.
[2] Due to the radiation exposure associated with the CT scan, base case analysis assumes that the annualised usage of surveillance with CT scan is lower in the current practice than recommended in the clinical guidelines such as EviQ (https://www.eviq.org.au/).

The applicant's pre-ESC response requested clarification regarding why in Table 15 the reduction in the number of CT scans performed is lower than the estimated number of MRI scans that would be performed under this item number (for example, 584 vs 842 in year 1). The rejoinder clarified that this was because the DCAR assumed that due to the radiation exposure associated with CT scans, the annual usage of surveillance with CT scan would likely be lower than the current practice recommended in clinical guidelines such as EviQ because of concerns about the potential lifetime accumulation of radiation. Therefore the DCAR does not assume a direct 1:1 relationship between the number of people who could access the proposed items and the number of people who currently receive CT surveillance scans, but that a proportion of the people who will access the MRI items will have been accessing CT scans in the past, and in this case, these CT scans will be replaced by MRI into the future.

Sensitivity analyses were performed to test the impact of the uncertainties (Table 15). Results were sensitive to the annual usage; higher usage value resulting in higher costs to the MBS.

Table 15 Sensitivity analysis

	2023	2024	2025	2026	2027	2028
Base case						
Net costs to MBS	**$253,421**	**$256,734**	**$260,016**	**$263,154**	**$266,138**	**$269,181**
Net copayments	**$37,113**	**$37,598**	**$38,078**	**$38,538**	**$38,975**	**$39,420**
Annual usage: 18% (base case 36%)						
Net costs to MBS	$73,818	$74,782	$75,738	$76,652	$77,522	$78,408
Net copayments	$9,225	$9,346	$9,465	$9,580	$9,688	$9,799
Annual usage: 25% (base case 36%)						
Net costs to MBS	$102,524	$103,864	$105,192	$106,462	$107,669	$108,900
Net copayments	$12,813	$12,981	$13,147	$13,305	$13,456	$13,610
Annual usage: 50% (base case: 36%)						

	2023	2024	2025	2026	2027	2028
Base case						
Net costs to MBS	**$253,421**	**$256,734**	**$260,016**	**$263,154**	**$266,138**	**$269,181**
Net copayments	**$37,113**	**$37,598**	**$38,078**	**$38,538**	**$38,975**	**$39,420**
Net costs to MBS	$443,408	$449,203	$454,945	$460,436	$465,657	$470,981
Net copayments	$67,707	$68,592	$69,468	$70,307	$71,104	$71,917
Annual usage: 72% (base case: 36%)						
Net costs to MBS	$743,385	$753,101	$762,728	$771,933	$780,687	$789,613
Net copayments	$116,013	$117,529	$119,032	$120,468	$121,834	$123,227
Proportion of patients receiving treatment: 5% (base case 10%)						
Net costs to MBS	$241,902	$245,064	$248,197	$251,192	$254,041	$256,945
Net copayments	$35,426	$35,889	$36,347	$36,786	$37,203	$37,629
Proportion of patients receiving treatment: 15% (base case 10%)						
Net costs to MBS	$264,941	$268,403	$271,835	$275,115	$278,235	$281,416
Net copayments	$38,799	$39,307	$39,809	$40,289	$40,746	$41,212
Current annualised usage of CT scan: 15% (base case 25%)						
Net costs to MBS	$348,765	$353,323	$357,840	$362,159	$366,265	$370,453
Net copayments	$53,945	$54,650	$55,348	$56,016	$56,652	$57,299
Current annualised usage of CT scan: 36.27% (base case 25%)						
Net costs to MBS	$145,969	$147,877	$149,768	$151,575	$153,294	$155,046
Net copayments	$18,143	$18,380	$18,615	$18,839	$19,053	$19,271
Proportion of ultrasound services offset by MRI: 10% (base case 0%)						
Net costs to MBS	$236,717	$239,810	$242,876	$245,807	$248,595	$251,437
Net copayments	$34,167	$34,614	$35,056	$35,479	$35,882	$36,292
Proportion of ultrasound services offset by MRI: 20% (base case 0%)						
Net costs to MBS	$220,012	$222,887	$225,737	$228,461	$231,051	$233,693
Net copayments	$31,222	$31,630	$32,034	$32,421	$32,788	$33,163
Proportion of CT scans offset by MRI: 80% (base case 100%) [1]						
Net costs to MBS	$218,373	$221,227	$224,055	$226,759	$229,330	$231,952
Net copayments	$32,208	$32,629	$33,046	$33,445	$33,824	$34,211
Proportion of CT scans offset by MRI: 60% (base case 100%) [1]						
Net costs to MBS	$197,868	$200,454	$203,017	$205,467	$207,797	$210,172
Net copayments	$29,645	$30,033	$30,417	$30,784	$31,133	$31,489
Fee per MRI: $450 (base case: $637.25)						
Net costs to MBS	$112,951	$114,428	$115,890	$117,289	$118,619	$119,975
Net copayments	$19,938	$20,198	$20,457	$20,704	$20,938	$21,178
Fee per MRI: $900 (base case: $637.25)						
Net costs to MBS	$474,629	$480,833	$486,980	$492,857	$498,445	$504,144
Net copayments	$37,113	$37,598	$38,078	$38,538	$38,975	$39,420
Fee for contrast: $120 (base case: $45.50)						
Net costs to MBS	$301,422	$305,362	$309,265	$312,998	$316,547	$320,166
Net copayments	$45,561	$46,156	$46,746	$47,311	$47,847	$48,394
Fee per CT scan: $374.60 (base case: $480.56)						
Net costs to MBS	$305,972	$309,971	$313,934	$317,722	$321,325	$324,999
Net copayments	$46,396	$47,003	$47,604	$48,178	$48,724	$49,281

	2023	2024	2025	2026	2027	2028
Base case						
Net costs to MBS	**$253,421**	**$256,734**	**$260,016**	**$263,154**	**$266,138**	**$269,181**
Net copayments	**$37,113**	**$37,598**	**$38,078**	**$38,538**	**$38,975**	**$39,420**
Fee per CT scan: $499.50 (base case: $480.56)						
Net costs to MBS	$243,997	$247,186	$250,346	$253,367	$256,240	$259,170
Net copayments	$35,484	$35,947	$36,407	$36,846	$37,264	$37,690
Proportion of MRI scans using contrast agent: 70% (base case: 90%)						
Net costs to MBS	$246,914	$250,141	$253,339	$256,396	$259,303	$262,268
Net copayments	$35,959	$36,429	$36,895	$37,340	$37,763	$38,195
Proportion of MRI scans using contrast agent: 100% (base case: 90%)						
Net costs to MBS	$256,675	$260,030	$263,354	$266,532	$269,555	$272,637
Net copayments	$37,689	$38,182	$38,670	$39,137	$39,580	$40,033
GPG set on 1 November 2022: $93.20 (base case: $87.20 set on 1 November 2021)						
Net costs to MBS	$248,959	$252,213	$255,438	$258,520	$261,452	$264,441
Net copayments	$41,575	$42,118	$42,656	$43,171	$43,661	$44,160

CT = computed tomography; GPG = greatest permissible gap; MBS = Medicare Benefits Schedule; MRI = magnetic resonance imaging

15. Other relevant information

Contrast-enhanced ultrasound (CEUS)

CEUS is not widely used in Australia, however, considering the low risk of nephrotoxicity and at least noninferior diagnostic accuracy to CECT and CE-MRI, CEUS can be an effective alternative for differential diagnosis of RCC (see section 5 in the main body of the report). However, some important limitations to the use of CEUS are time and resource constraints due to it being more time consuming and labour intensive than CT and being operator-dependent. With the shortage of sonographers in Australia, access to CEUS is currently limited.

However, MRI may also not be readily accessible in the emergent setting. There are a number of reasons that are likely to limit the number of MRI services conducted in Australian clinical practice including:

- Image acquisition is slower than CT
- There is a requirement for safety screening
- There is a paucity of MRI scanners and slow image acquisition.

Sustainability of MRI and CT

Both MRI and CT have much higher carbon emissions than US, with MRI responsible for nearly twice as much carbon emission per scan as CT. Much of the energy consumption comes from standby mode and from the associated cooling mechanisms required to run the machines. The contamination of the environment by the contrast agents used in imaging (gadolinium and iodine) is also a consideration, although the health effects of this are still somewhat unclear.

The proposed MBS item will increase demand for MRI such that more MRI machines may be required; this will increase the environmental impact, which comes from the energy used for the scan, including the machine itself and the associated cooling systems.

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical and item descriptor issues:

- ESC agreed that rather than listing eligible genetic conditions in the item descriptor, as proposed by the applicant, the item descriptor should be generic with an accompanying explanatory note to assist clinicians in determining patient eligibility.
- There was insufficient evidence to draw any conclusions on the comparative accuracy of MRI and ultrasound (US) or the change in clinical management for MRI vs CT or US.
- A non-systematic literature search supported the claim of superior safety of abdominal MRI compared with abdominal CT. MRI likely has superior safety to CT, and clinicians are recommending MRI scans for patients in preference to CT scans.
- The evidence did not show a significant difference in the accuracy of MRI, either with or without contrast, compared to CT in imaging angiomyolipomas and renal cell carcinomas. This combined with the lack of evidence on the comparative accuracy of MRI vs US or the change in clinical management for MRI vs CT or US meant that overall the impact of MRI over CT or US in the clinical management of patients with the exemplar syndromes of Tuberous Sclerosis Complex or Von Hippel-Lindau disease is uncertain.
- Abdominal MRI is likely to replace CT but not US in clinical practice. US is an inexpensive and safe methodology that is readily accessible and suitable for initial imaging of the kidneys, especially in children.

Economic issues:

- The model assumes that surveillance starts at age 20 but surveillance guidelines recommend starting surveillance at an earlier age. Specifying a lower starting age in the model will have significant impact on radiosensitivity and therefore a larger impact on cancers averted by switching to MRI.
- The approach used to estimate radiation-induced cancers based on an incidence rate ratio probably results in an underestimate. A biological effects of ionising radiation (BEIR) VII coefficient estimates approach may be more appropriate. However, it was acknowledged that developing a more complex model was unnecessary as it would be unlikely to change the interpretation of the ICER.
- The economic model counts the number of radiation induced cancers avoided in the ICER denominator and also offsets the excess healthcare costs of these avoided cancers in the ICER numerator. ESC preferred that 'radiation induced cancer avoided' is interpreted as an event bundle of both health resource costs and health outcomes. However the Assessment Group noted that they intended 'radiation induced cancer avoided' to be interpreted as constituting only health outcomes and have produced an Addendum to clarify these issues. *Note: Reflecting MSAC advice, the Addendum referred to here has been removed from this publication.*
- The results of the model are very sensitive to the modelled time horizon and discounting as the costs and outcomes associated with the radiation induced cancers are over a lifetime and a shorter time horizon cannot capture these impacts. This is because excess cancer risk and costs are higher towards the later years due to increase in the cumulative dose of CT scan radiation and lags in the dose-cancer induction.

Financial issues:

- There is no current usage data of the specific form of CT scanning that would be replaced by this new service since the relevant MBS item is generic, so the financial modelling had to rely on an epidemiological approach.

Other relevant information:

- The proposed items are for a small, defined population diagnosed with a rare genetic condition with a significant clinical need for the proposed service and where there was low availability of high-quality data on effectiveness. This is similar to Application 1668 where greater weight was placed on consideration of the international and domestic guidelines for management of the target population, and the relatively small and highly targeted financial impacts of the application.

ESC discussion

ESC noted that this was an application from Rare Voices Australia requesting a Medicare Benefits Schedule (MBS) listing of abdominal magnetic resonance imaging (MRI) for the purposes of annual surveillance to detect newly developed renal tumours and the assessment of changes over time to the renal tumour in patients with rare inherited conditions associated with an increased risk of renal tumours.

ESC noted that the proposed population for this application is a heterogenous group of 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. There are eight identified conditions, but ESC noted that patients with other rare genetic disorders associated with the increased risk of developing renal tumours are also intended to be eligible for this service. ESC noted that genetic testing for heritable kidney diseases, including those in scope for this application, is currently available through Medicare.

ESC noted the consumer feedback and recognised there may be equity of access issues to MRI for people in remote and regional areas. ESC also noted that many international guidelines recommend MRI as the imaging modality for the proposed services. ESC noted that improved monitoring and surveillance can result in peace of mind for families and aids in planning for support services, and that there is also value in identifying the absence of disease, or disease stabilisation.

ESC also noted consultation feedback that requested multiple organ surveillance, not just kidneys. ESC noted that the proposed conditions comprise 5% of benign and malignant renal tumours, and that the proposed MBS descriptor covers other conditions with increased risk of renal tumours, not just the eight specific conditions listed. ESC also noted that there is an MRI item (63440) that allows for MRI scanning of the abdomen in children under 16 years of age for a pelvic or abdominal mass. Genetic testing for these conditions is also on the MBS, and many patients that require surveillance will have already been identified, either through genetic testing or by clinical phenotype.

ESC noted that the application proposes two new MBS items for two distinct populations:

- PICO set 1 (population 1), for surveillance of patients with confirmed clinical or molecular diagnosis of a condition that results in a high risk of developing renal tumours
- PICO set 2 (population 2), for patients diagnosed with a syndrome associated with increased risk of kidney cancer who require monitoring 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.

ESC noted that the descriptors' frequency of testing of every 12 months for population 1 and every 3 months for population 2 is appropriate and aligns with clinical guidelines on monitoring recommendations.

ESC agreed with the suggestion that instead of defining access to these items in terms of an exclusive list of rare genetic conditions access be defined as being for patients with a confirmed clinical and/or molecular diagnosis of a rare genetic disorder associated with a >N% risk of

developing renal tumours where the value of the risk threshold (N%) will be determined through consultation with clinical experts prior to implementation of the proposed items. ESC noted the generic item descriptor would be accompanied with an explanatory note to assist clinicians in determining patient eligibility. Figures 1-3 show the draft item descriptions and associated explanatory note as supported by ESC.

Figure 1 - Proposed annual surveillance item (PICO set 1)

Category 5 – Diagnostic Imaging Services
Item XXXX MRI – scan of the abdomen, requested by a specialist or consultant physician, to assess the development and/or growth of renal tumours in patients with a confirmed clinical and/or molecular diagnosis of a genetic disorder associated with an increased risk of developing renal tumours. For any particular patient – applicable not more than once in a 12 month period. *Restricted to one scan per 12 months.* (R) (Anaes) (Contrast) **Fee:** $637.25

Figure 2 - Proposed tumour monitoring item (PICO set 2)

Category 5 – Diagnostic Imaging Services
Item YYYY MRI – scan of the abdomen, requested by a specialist or consultant physician, to assess a patient with a known renal tumour who has: d) a confirmed clinical and/or molecular diagnosis of a genetic disorder associated with an increased risk of developing renal tumours, and e) 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 XXXX; or f) 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) **Fee:** $637.25

Figure 3 - Proposed explanatory note to accompany items XXXX and YYYY

For Items XXXX and YYYY, access to these items is for patients with a confirmed clinical and/or molecular diagnosis of a rare genetic disorder associated with a >N% risk of developing renal tumours. Examples of such disorders could include: • 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.

ESC noted that the current clinical management algorithm for screening the populations is highly variable; there are differing guidelines for the different groups and they currently all use a combination of MRI, computed tomography (CT) scanning and ultrasound (US) across differing periodic surveillance (dependent on the condition). ESC noted that abdominal US (MBS item

55036) is an inexpensive and safe methodology that is readily accessible and suitable for initial imaging of the kidneys, especially in children, to determine the presence of any cystic or solid lesions. Although US was a comparator in the PICO Confirmation ratified by PASC, ESC considered that MBS funding of abdominal MRI is very unlikely to affect the current use of US. But, where confirmatory imaging is required after an US, ESC considered that the test would most likely be MRI instead of CT. ESC concluded that abdominal MRI is likely to replace CT but not US in clinical practice.

The clinical claim made by the applicants is that the use of abdominal MRI is:

- superior in terms of safety as it is associated with decreased adverse effects compared to CT
- superior in terms of effectiveness as it provides an overall benefit in mortality through reduction in catastrophic bleeding from angiomyolipomas (AMLs) and improved outcomes from malignant tumours through early diagnosis.

ESC noted that the clinical evidence for population 1 was from 23 studies and 2 systematic reviews for assessing MRI accuracy in detecting renal tumours compared to US or CT. For population 2, the evidence was from two studies that compared MRI to CT, but no studies were found that compared MRI and US. No studies were identified that assessed the change in clinical management for MRI compared with either US or CT for either population. There was also insufficient evidence to draw any conclusions on the comparative accuracy of MRI and US.

As no comparative safety studies were identified, ESC noted that general safety information related to the three imaging modalities (MRI, CT and US), including information from authoritative information websites and clinical guidelines, and the results of an additional, non-systematic literature search, were considered instead. ESC noted that there is a known risk of radiation exposure with CT. ESC also noted that there are known risks associated with the contrast agents used for both MRI and CT, although the risk is low (in particular with MRI). However, ESC noted that patients with kidney disease are at greater risk of harm from iodine-containing contrast used for CT. The contrast media can temporarily worsen kidney function in patients with existing severely impaired kidney function. Occasionally, the damage can be prolonged and may require treatment with dialysis. ESC considered that, since the target populations are more likely to have renal disease than the general population, these safety concerns are relevant. ESC also noted that it is standard practice for all patients at risk of kidney disease who are undergoing CT or MRI to have their kidney function assessed by their clinician prior to receiving contrast. ESC considered that MRI likely has superior safety to CT, and noted that clinicians are recommending MRI for patients in preference to CTs.

For population 1, ESC noted the pre-ESC response, in which the applicant stated that some evidence of superiority for MRI does exist for specific circumstances, particularly in the assessment of fat-poor AMLs (with diffusion weighted magnetic resonance imaging). In clinical practice, these differences in AMLs help avoid the need for biopsy or surgical intervention.[3] However, overall ESC considered that the evidence did not show a significant difference in the accuracy of MRI, either with or without contrast, compared to CT in imaging AMLs and renal cell carcinomas (RCCs). As noted previously, there was also insufficient evidence to draw any conclusions on change in clinical management for MRI compared with either US or CT. As the diagnostic accuracy of MRI was noninferior to CT, ESC considered that only a small number of patients would be expected to have a change in diagnosis leading to a change of management with respect to RCC or AML at risk of causing complications. Thus, ESC considered that the impact of MRI over CT or US on the clinical management of patients with the exemplar

[3] Northrup H, et al. (2021). Updated international tuberous sclerosis complex diagnostic criteria and surveillance and management recommendations. *Pediatric Neurology,* 123:50–66.

syndromes of tuberous sclerosis complex (TSC) or Von Hippel-Lindau disease (VHL) and associated health outcomes to be uncertain.

Similarly for population 2, ESC considered that the small volume of evidence on the use of MRI for monitoring changes to renal tumours over time was considered insufficient to draw any conclusions on the comparative effectiveness of one imaging modality compared over another.

Overall, ESC therefore considered that the claim of superior effectiveness of MRI compared to US or CT was not met. However, ESC recognised that information from authoritative websites and clinical guidelines, and evidence from five studies found in an additional, non-systematic literature search, supported the claim of superior safety of abdominal MRI compared with abdominal CT.

ESC noted that as no comparative evidence was found related to the proposed use of abdominal MRI versus CT scan for the assessment of response to treatment or tumour growth, the economic evaluation did not extend to population 2 but only considered population 1. ESC also noted that due to the sparseness of evidence using the two exemplar conditions (TSC and VHL) US was not included as a comparator in the economic evaluation. ESC considered that these two limitations in the economic modelling in light of the sparseness of evidence were reasonable.

For population 1, the economic evaluation was a cost-effectiveness analysis with a Markov model which relied on the superior safety claim of MRI when compared to CT, due to a reduced exposure to ionising radiation associated with CT scans. This resulted in an ICER outcome that estimated the cost per radiation-induced cancer avoided.

ESC noted that the economic model compared the scenarios where lifetime active surveillance is performed using abdominal MRI, to scenarios where CT imaging is used and assumed that the average rate of surveillance is one imaging scan every 24 months. The risk associated with the exposure to ionising radiation with CT scans is included as the incidence of radiation-induced cancer in the model (for MRI this exposure is assumed to be zero). ESC noted that the model estimated this excess cancer risk associated with the cumulative radiation exposure from CT imaging based on an incidence rate ratio (IRR) for those exposed versus unexposed to CT imaging as reported by Mathews (2013)[4]. ESC queried whether the imaging techniques in this study reflected contemporary CT practice which lowers radiation dose with iterative reconstruction methods.

The base case was generated by a stepped evaluation, with two health states – alive or dead from radiation-induced cancer – over a 50-year time horizon. ESC noted that the model generated a base case incremental cost-effectiveness ratio (ICER) of $61,888 per radiation-induced cancer avoided.

ESC considered the approach used to estimate excess cancer risk associated with the cumulative radiation exposure from CT imaging may result in an underestimate because radiation dose, age or gender were not considered, but relies on the incidence rate ratio (IRR) derived from one study. ESC noted that the model used an entry age of 20 years, which it considered to be too high given that surveillance guidelines recommend starting surveillance at an earlier age. Specifying a lower starting age in the model will have significant impact on radiosensitivity and therefore a larger impact on cancers averted by switching to MRI.

[4] Mathews J, et al. (2013). Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. *BMJ*, vol. 346, May 21: f2360.

ESC considered that a biological effects of ionising radiation (BEIR) VII coefficient estimates approach[5] would have been a more appropriate means of estimating excess cancer risk associated with cumulative radiation exposure as this method can determine the number of cancers directly attributable to a single abdominal or pelvic CT scan for males and females, by age at scan, as well as differentiate by organ, to determine excess cancers. This approach demonstrates a significant increase in cancers when CT scanning is initiated at younger ages. ESC acknowledged this approach would have been more complicated but more accurate, and considered that the approach used in the Department-contracted assessment report (DCAR) potentially underestimated the risk of cancers. ESC noted that the BEIR VII method was extensively used in the literature. For example ESC noted that in Kang et al. (2014)[6] an organ-specific radiation-risk model based on BEIR VII methods was used to determine life expectancy losses attributable to radiation-induced cancers in hypothetical patients undergoing CT versus MRI surveillance of Bosniak IIF lesions for up to 5 years, accounting for potential lesion progression and treatment. This model had more states than the DCAR model. However, ESC acknowledged that developing a more complex model was unnecessary as it would be unlikely to change the interpretation of the ICER.

ESC noted that other features of the model were:

- diagnostic accuracy of the two forms of imaging was not included in the base case given the evidence found no conclusive difference in the accuracy of MRI compared to CT at imaging AMLs and RCCs
- patients were assumed to be susceptible to death from background and disease-specific causes at all times which ESC considered to be appropriate
- prior investigations were assumed to be the same irrespective of the diagnostic pathway chosen in the base case

ESC also noted that in the model, CT-exposed patients were assumed to incur a one-off excess healthcare cost of $46,346 associated with radiation induced cancers in the first year of imaging based on the average cost for the initial phase of cancer reported by Goldsbury et al. (2018)[7]. ESC noted that there were problems associated with this one-off excess healthcare cost as it did not allow for:

- Differentiation in phase of care phase (initial, continuing, terminal)
- Radiation induced cancers in subsequent years of imaging
- Differentiation by type of cancer (Goldsbury reported considerable variation by cancer type (range: $9,708–$66,316 2021 AUD)).

However ESC questioned the inclusion of the excess healthcare cost associated with radiation-induced cancer in the ICER estimate as a cost which was avoided in the MRI arm of the model leading to a lower cost being reported in the numerator of the ICER. ESC's concern was motivated by the framing of the ICER measure in the model as "cost per radiation-induced cancer avoided" as ESC considered whether 'radiation-induced cancer avoided' should be an event bundle inclusive of all resource costs associated with the cancer as well as the health outcomes of the cancer or just the health outcomes. ESC considered that if 'radiation-induced cancer avoided' was defined to be inclusive of resource costs as well as health outcomes then it should

[5] Maxwell S, et al. (2019). How have advances in CT dosimetry software impacted estimates of CT radiation dose and cancer incidence? A comparison of CT dosimetry software: Implications for past and future research. *PLoS One* Aug 14;14(8):e0217816.

[6] Kang S, et al. (2014). Microsimulation model of CT versus MRI surveillance of Bosniak IIF renal cystic lesions: should effects of radiation exposure affect selection of imaging strategy? *AJR Am J Roentgenol*, 203(6): W629-636.

[7] Goldsbury D, et al. Health services costs for cancer care in Australia: Estimates from the 45 and Up Study. *PLoS One* Jul 30; 13(7): e0201552.

be inclusive of excess healthcare costs, which therefore should not be treated as a cost avoided by the use of MRI, creating a cost offset in the ICER's numerator.

Note:

In line with MSAC advice this section has been amended. The details of the reanalysis requested by ESC originally described in this box including an Attachment have been removed and have been incorporated into Section 13 of this document.

ESC noted that the results of the model are very sensitive to the modelled time horizon and discounting as the costs and outcomes associated with the radiation induced cancers are over a lifetime and a shorter time horizon cannot capture the impacts of these cancers adequately. For example ESC noted that a reduction in the time horizon to 20 years led to a much higher ICER of $574,263 while a 0% discount rate led to MRI dominating CT. This is because excess cancer risk and costs are higher towards the later years due to increases in the cumulative dose of CT scan and lags in the dose-cancer induction.

ESC noted the scenario analysis where imaging accuracy was included to differentiate malignant and benign RCCs, which produced a much reduced ICER of $25,690 per radiation-induced cancer avoided. This analysis integrates median values for sensitivity and specificity for CT and MRI and subsequent diagnostic and treatment costs (VHL as an exemplar). ESC noted that test performance estimates are from mixed sources and are imprecise, with overlapping confidence intervals; therefore, ESC considered these findings to be highly uncertain and should be interpreted with caution.

ESC noted that, since there are no current usage data available for the comparator services due to the generic nature of the item for CT scans, an epidemiological approach was used to estimate the financial implications of funding the proposed MRI services. The financial analysis assumed that routine screening will end by the time the patients turn 70 years of age. ESC considered that the assumptions underlying the financial analysis were reasonable and clearly justified. ESC noted that the current applicable greatest permissible gap (GPG) as of November 2022 was $93.20 which would result in an out-of-hospital benefit for the two proposed services of $544.05 ($637.25–$93.20) whereas the GPG applied in the base case in the DCAR was $87.90. The GPG is indexed annually in November and MRI services are indexed annually in July. However, due to the small population sizes, ESC considered that these changes will not significantly impact the financials. This was demonstrated in the DCAR's sensitivity analysis which accounted for the current greatest permissible gap (GPG), resulting in the cost of MRI services to the MBS being $248,959 in Year 1 to $264,441 in Year 5 (see Table 16).

ESC noted that contrast-enhanced ultrasound (CEUS) could address concerns about the intravenous contrast agent. CEUS is at least non-inferior and possibly superior to CT with contrast and MRI with contrast in terms of accurately diagnosing malignant versus benign renal lesions when compared to a histopathology reference standard. However, ESC noted that CEUS is not widely used in Australia due to a lack of availability of sonographers.

ESC noted that the limited availability of MRI in some settings could lead to equity of access issues. ESC noted that the carbon footprint of MRI is greater than that for CT or US.

In addition, ESC noted that MSAC has previously considered and supported a similar MSAC application (PSD, Application 1668) for whole body MRI in individuals with 17p deletion syndrome in July 2022. At that time, MSAC had considered that, as there was a low availability of high-quality data due to the small patient population, an accurate estimate of cost-effectiveness was not possible. Greater weight was therefore placed on consideration of the international and domestic guidelines for management of the target population, and the relatively small and highly targeted financial impacts of the application.

17. Applicant comments on MSAC's Public Summary Document

We are pleased with the outcome of this application and the recognition of the challenges for Australians living with a rare disease. The outcome will make a positive difference for families living with these rare and ultra-rare conditions and the approach of the Committee in responding to nature of rare conditions is welcomed.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website