



Australian Government

Medical Services Advisory Committee

## Public Summary Document

### ***Application No. 1528 – Somatic tumour gene testing for the diagnosis of renal cell carcinoma, hydatidiform moles, granulosa cell ovarian tumour, salivary gland tumours, and secretory carcinoma of the breast***

**Applicant:** The Royal College of Pathologists of Australasia (RCPA)

**Date of MSAC consideration:** MSAC 77<sup>th</sup> Meeting, 28-29 November 2019  
MSAC 76<sup>th</sup> Meeting, 1-2 August 2019

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

#### **1. Purpose of application**

##### *November 2019 MSAC consideration*

MSAC considered the following key questions/concerns raised by the Department for somatic tumour gene testing for the assessment of hydatidiform mole:

- The appropriate wording of the Medicare Benefits Schedule (MBS) item descriptor, including the proposed restrictions and the Applicant's proposed fees for gene testing in patients with hydatidiform mole.

##### *August 2019 MSAC consideration*

An application for MBS listing of a specified number of genetic tests for the diagnosis of a number of rare cancer sub-types was received from the Royal College of Pathologists in Australasia (RCPA) by the Department of Health.

The proposed medical services would provide genetic testing for:

- characterisation of ploidy status by short tandem repeat (STR) genotyping or fluorescent in-situ hybridisation (FISH) in the assessment of hydatidiform mole
- identification of *FOXL2* 402C>G status in granulosa cell ovarian tumour
- identification of *NUTM1* gene status at 15q14 by FISH for the diagnosis of NUT midline carcinomas
- identification of *ETV6-NTRK3* gene status in a patient with secretory carcinoma of the breast
- identification of *MALM2* gene status for the diagnosis of mucoepidermoid carcinoma of the salivary gland
- identification of *EWSR1* or *PLAG1* gene status for the diagnosis of hyalinising clear cell carcinoma of the salivary gland
- identification of *TFE3* or *TFEB* gene rearrangement in the assessment of a patient with renal cell carcinoma.

This application was considered in conjunction with Applications 1526 and 1527.

## **2. MSAC's advice to the Minister– November 2019 consideration**

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported the creation of a new MBS item for hydatidiform mole testing that is pathologist determinable, with a fee of \$340.

### **Consumer summary**

The Royal College of Pathologists of Australasia (RCPA) applied for public funding through the Medicare Benefits Schedule (MBS) for genetic testing of hydatidiform mole. This application is part of a combined application for several genetic tests used to diagnose a number of rare cancers (Applications 1526-1527-1528).

A hydatidiform mole is a clump of sacs full of fluid that forms when something goes wrong during fertilisation (when a sperm and egg join together to create an embryo). It is also sometimes called a molar pregnancy. Molar pregnancies often end in miscarriage. Genetic testing on a piece of tissue from a hydatidiform mole can help doctors provide women with targeted treatment, and advice about when it is safe to become pregnant again.

### **MSAC's advice to the Commonwealth Minister for Health**

MSAC supported creating a new MBS item for hydatidiform mole genetic testing, with the same fee as other genetic tests for rare cancers.

## **Summary of consideration and rationale for MSAC's advice – November 2019**

MSAC noted that this genetic test relates to determining the presence or absence of a pre-neoplastic process (not a “tumour” as stated in the draft item descriptor). MSAC noted that the exclusion of hydatidiform mole is one of the main reasons why products of conception (miscarriage specimens) are sent for histopathological examination. The clinical utility relates to changes in patient management based on the result (follow-up testing and avoidance of pregnancy for a defined period).

MSAC noted that this is one item of Application 1528 that was considered at the August 2019 meeting. At that meeting MSAC considered that Application 1528 should be re-visited because it did not adequately address either the likelihood of recurring disease needing repeat testing (and thus the increased possibility of false negative clinical conclusions) or the need for samples from the parental source.

MSAC noted that the term “tumour” is incorrect and that the appropriate wording is “product of conception”. MSAC agreed that “clinical or laboratory evidence of” was not needed, nor was it a requirement that the parental source be identified. MSAC also noted that the test should be pathologist-determinable and therefore “specialist or consultant physician” was not necessary in the item descriptor.

MSAC noted that the estimated number of tests was based on “confirmed” molar pregnancies per annum (around 500); however, the likely cases tested may be 3–4-fold greater. MSAC noted that the likelihood of false negatives means that the test might need to be done multiple times, so the limitation should be once per pregnancy rather than once per lifetime.

MSAC noted that the price for this test should align with those in Applications 1526 and 1527 as they are equivalent in complexity. Therefore, MSAC set the fee at \$340 in line with the items in those applications.

MSAC supported the following MBS item descriptor:

XXXXX-12

Analysis of products of conception from a patient with suspected hydatidiform mole for the characterisation of ploidy status.

Maximum one test per pregnancy episode.

Fee: \$340

### ***Other discussion***

It was noted that MSAC applications 1526 and 1527 (which were supported at MSAC's August 2019 meeting) also need amendments in their descriptors, to ensure that they are also pathologist-determinable. The Department will follow-up to ensure that this is the case.

### **3. MSAC's advice to the Minister – August 2019 consideration**

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported 17 of the 19 requested MBS items proposed by the MSAC Executive overall. Two requested MBS items were deferred, relating to hydatidiform mole) and analogue secretory carcinoma, in order to seek more information in order to clarify the appropriate test usage and item descriptor wording.

#### **Consumer summary**

Cancer arises when cells develop genetic changes that cause abnormal growth. A somatic cell is any cell in the body that is not an egg or sperm cell, and gene mutations which develop in cells after the egg is fertilised are called "somatic mutations". Somatic tumour testing is where a piece of a tumour is tested to look at the somatic mutations in the cancer cells. These tests can help provide patients with appropriate, targeted treatment, or advice about the outcome of their disease.

Applications 1526, 1527 and 1528 are for somatic tumour testing for rare cancers. They have been grouped together because the numbers of patients with each of these cancers is too small to consider each application on its own.

#### **MSAC's advice to the Commonwealth Minister for Health**

MSAC recommended some changes to the wording in the MBS item descriptors, to ensure consistency and appropriate setting of fees when testing for these somatic gene mutations.

MSAC supported the following listings for Application 1528:

Category 6 – (Group P7 Genetics) – Pathology services
<p>XXXXX-13</p> <p>Analysis of tumour tissue from a patient with clinical or laboratory evidence, including morphological features, of granulosa cell ovarian tumour, as requested by a specialist or consultant physician, for the detection of FOXL2.402C&gt;G status.</p> <p>Maximum one test per lifetime</p> <p>Fee: \$250</p>
<p>XXXXX-14</p> <p>Analysis of tumour tissue from a patient with clinical or laboratory evidence, including morphological features, of midline NUT carcinoma, as requested by a specialist or consultant physician, for the characterisation of <i>NUTM1</i> gene status at 15q14.</p> <p>Maximum one test per lifetime</p> <p>Fee: \$340</p>
<p>XXXXX-15</p> <p>Analysis of tumour tissue from a patient with clinical or laboratory evidence, including morphological features, of secretory carcinoma of the breast, as requested by a specialist or consultant physician, for the characterisation of <i>ETV6-NTRK3</i> gene rearrangement.</p> <p>Maximum one test per lifetime</p> <p>Fee: \$340</p>
<p>XXXXX-16</p> <p>Analysis of tumour tissue from a patient with clinical or laboratory evidence, including morphological features, of mucoepidermoid carcinoma, as requested by a specialist or consultant physician, for the characterisation of <i>MALM2</i> gene rearrangement.</p> <p>Maximum one test per lifetime</p> <p>Fee: \$340</p>
<p>XXXXX-17</p> <p>Analysis of tumour tissue from a patient with clinical or laboratory evidence, including morphological features, of mammary analogue secretory carcinoma of the salivary gland, as requested by a specialist or consultant physician, for the characterisation of <i>ETV6-NTRK3</i> gene rearrangement.</p> <p>Maximum one test per lifetime</p> <p>Fee: \$340</p>
<p>XXXXX-18</p> <p>Analysis of tumour tissue from a patient with clinical or laboratory evidence, including morphological features, of hyalinising clear cell carcinoma of the salivary gland, as requested by a specialist or consultant physician, for the characterisation of <i>EWSR1</i> rearrangement with or without <i>PLAG1</i> gene rearrangement.</p> <p>Maximum one test per lifetime</p> <p>Fee: \$400</p>

Category 6 – (Group P7 Genetics) – Pathology services

XXXXX-19

Analysis of tumour tissue from a patient with clinical or laboratory evidence, including morphological features, of renal cell carcinoma, as requested by a specialist or consultant physician, for the characterisation of gene rearrangements in:

- a) *TFE3*;and/ or
- b) *TFEB*.

Maximum one test per lifetime

Fee: \$400

#### 4. Background

MSAC noted that the proposals for 19 new MBS items from the MSAC Executive spanned three applications:

- Application No. 1526 – Somatic gene testing of haematological malignancies
- Application No. 1527 – Somatic gene testing of central nervous system tumours and sarcomas
- Application No. 1528 – Somatic gene testing of hydatidiform mole, granulosa cell tumour of the ovary, midline squamous cell carcinoma, salivary gland carcinoma, secretory carcinoma of the breast and renal cell carcinoma.

MSAC noted that there has been a long history of meetings for these applications. The requested MBS items are for rare tumours with low pathogenic variant frequencies, so they have been pragmatically grouped together.

MSAC affirmed the importance of ensuring that appropriate quality assurance programs are established for all gene testing as part of the implementation of the proposed MBS items.

MSAC noted that its task is to check that each item descriptor is appropriate. The RCPA has had its feedback already incorporated into the proposed descriptors.

MSAC advised the following as being applicable across all relevant MBS items:

- for testing for a rearrangement in a single gene, the fee should be \$340 (reflecting a slightly higher fee than the MBS item number for ISH for HER2 and in doing so establishing a benchmark); for a panel testing 2–3 genes, the fee should be \$400 (reflecting the lowest requested fee for testing 3 genes); and for a panel testing 4 or more genes, the fee should be \$800 (reflecting the lowest requested fee for testing 4 or more genes)
- if a descriptor is referring to a single gene, then write the gene into the text (not in a bulleted list)
- if it is referring to more than one gene, then write the genes in a list without the word “or” between each gene
- change “characterisation of one or more of the following gene rearrangements” to “characterisation of gene rearrangements in one or more of the following” and remove the word “or” between each gene in the list that follows
- change “mutation” to “pathogenic variant”
- state that there is a maximum of one test per lifetime.

In addition to the above changes, the following specific amendments were proposed:

- XXXXX-01 – “laboratory evidence” should be defined as being “not negative on immunohistochemistry”
- XXXXX-01 – this item cannot be co-claimed with XXXXX-02, so a note to this effect should be added
- XXXXX-02 – this item cannot be co-claimed with XXXXX-01, so a note to this effect should be added
- XXXXX-04 – change “the characterisation of i(q7) gene rearrangement” to “the presence of isochromosome 7q”.
- XXXXX-08 – keep “glioma or glioneural tumours” (not “oligodendroglioma”) and use “detection” instead of “characterisation”.
- XXXXX-13 – the fee should be benchmarked to the fee of \$250 (reflecting MBS items 73348 and 73350, which both specify the detection of known gene variants in diagnosing cystic fibrosis), and “characterisation” should be replaced with “detection”.

MSAC noted the Department’s concerns that the proposed descriptor for XXXXX-11 does not limit the number of genes that may be tested. While this permits the testing of a greater number of clinically relevant genes, this descriptor may lead to a risk of leakage for testing of gene pathogenic variants where there is no evidence of clinical utility. However, MSAC noted that a panel test will be required in most cases, and the costing of testing extra genes should not result in an increase beyond the recommended fee of \$800.

MSAC considered that XXXXX-17 appears to be a duplicate of XXXXX-15 for analogue secretory carcinoma, so needs to be removed or amended to clarify the intended difference.

MSAC considered that XXXXX-12 for hydatidiform mole should be re-visited because it did not adequately address either the likelihood of recurring disease needing repeat testing (and thus the increased possibility of false negative clinical conclusions) or the need for samples from the parental source.

MSAC advised that, as a general principle, these tests are for once in a lifetime. It was noted that some might patients may need another test if metastasis is present; however, MSAC did not support these items being used for monitoring. It is possible that, on relapse, retesting may be desirable. MSAC advised that this should not be accommodated now because MSAC could not support the consequential delay in implementing these applications for initial diagnosis.

## **5. Prerequisites to implementation of any funding advice**

Neither the PICO nor the MSAC Executive discussion addressed the regulatory and/or accreditation requirements associated with the provision of any of the proposed tests. The National Pathology Accreditation Advisory Council advised MSAC that the testing methodology by either FISH or microsatellite analysis is mature and that there is an external quality assurance program (EQA) available.

## **6. Proposal for public funding**

The PASC process was used for this application, but given the status of testing in the Australian context, the nature of the genetic tests proposed, and following discussions both at

the Pathology Pilot Meeting and by the MSAC Executive, a full HTA assessment was not undertaken.

The requested MBS item descriptors are presented in Table 1. The item descriptors suggested by the Department are presented in Table 2.

**Table 1: Proposed MBS item descriptors, per the application form**

Category 6 –Genetics P7
Proposed item descriptor
<p>Characterisation of ploidy status by STR genotyping or FISH in the assessment of hydatidiform moles.</p> <p><b>OR</b></p> <p>Identification of FOXL2 402C&gt;G status in the assessment of granulosa cell ovarian tumours.</p> <p><b>OR</b></p> <p>Identification of NUT gene status at 15q14 in a patient with a malignant head and neck or midline carcinoma for the diagnosis of NUT midline carcinomas.</p> <p><b>OR</b></p> <p>Identification of ETV6-NTRK3 gene status in a patient with secretory carcinoma of the breast or mammary analogue secretory carcinoma (MASC) of salivary glands.</p> <p>Fee: \$454 each</p> <p><b>OR</b></p> <p>In the assessment of malignant salivary gland tumours, identification of:</p> <ul style="list-style-type: none"> <li>• MALM2 gene status for the diagnosis of mucoepidermoid carcinoma <b>AND/OR</b></li> <li>• ETV6-NTRK3 gene status for the diagnosis of analogue secretory carcinoma <b>AND/OR</b></li> <li>• EWSR1 gene status for the diagnosis of hyalinising clear cell carcinoma.</li> </ul>
<p>Fee: \$454 (for each)</p> <p><b>OR</b></p> <p>Identification of TFE3 or TFEB gene rearrangement in the assessment of renal cell carcinoma.</p> <p>Fee: \$454 (for each)</p>

**Table 2: Department-suggested MBS item descriptors**

Category 6 –Genetics P7
XXXXX-12
<p>Analysis of tumour tissue from a patient with clinical or laboratory evidence of hydatidiform mole, as requested by a specialist or consultant physician, for the characterisation of ploidy status and parental source.</p> <p><b>Maximum one test per lifetime</b></p> <p>Fee: \$xxx.xx Benefit: 75% = \$xxx.xx 85% = \$xxx.xx.</p>
XXXXX-13
<p>Analysis of tumour tissue from a patient with clinical or laboratory evidence of granulosa cell ovarian tumour, as requested by a specialist or consultant physician, for the characterisation of one or more of the following gene mutation:</p> <p>a) FOXL2 402C&gt;G status.</p> <p><b>Maximum one test per lifetime</b></p> <p>Fee: \$xxx.xx Benefit: 75% = \$xxx.xx 85% = \$xxx.xx.</p>
XXXXX-14
<p>Analysis of tumour tissue from a patient with clinical or laboratory evidence of head and neck or midline carcinoma, as requested by a specialist or consultant physician, for the characterisation of <i>NUTM1</i> gene status at 15q4.</p> <p><b>Maximum one test per lifetime</b></p> <p>Fee: \$xxx.xx Benefit: 75% = \$xxx.xx 85% = \$xxx.xx.</p>

<p>Category 6 –Genetics P7</p> <p>XXXXX-15</p> <p>Analysis of tumour tissue from a patient with clinical or laboratory evidence of secretory carcinoma of the breast or mammary analogue secretory carcinoma, as requested by a specialist or consultant physician, for the characterisation of <i>ETV6-NTRK3</i> gene rearrangement.</p> <p>Maximum one test per lifetime</p> <p>Fee: \$xxx.xx Benefit: 75% = \$xxx.xx 85% = \$xxx.xx.</p>
<p>XXXXX-16</p> <p>Analysis of tumour tissue from a patient with clinical or laboratory evidence of mucoepidermoid carcinoma, as requested by a specialist or consultant physician, for the characterisation of <i>MALM2</i> gene rearrangement.</p> <p>Maximum one test per lifetime</p> <p>Fee: \$xxx.xx Benefit: 75% = \$xxx.xx 85% = \$xxx.xx.</p>
<p>XXXXX-17</p> <p>Analysis of tumour tissue from a patient with clinical or laboratory evidence of analogue secretory carcinoma, as requested by a specialist or consultant physician, for the characterisation of <i>ETV6-NTRK3</i> gene rearrangement.</p> <p>Maximum one test per lifetime</p> <p>Fee: \$xxx.xx Benefit: 75% = \$xxx.xx 85% = \$xxx.xx.</p>
<p>XXXXX-18</p> <p>Analysis of tumour tissue from a patient with clinical or laboratory evidence of hyalinising clear cell carcinoma, as requested by a specialist or consultant physician, for the characterisation of <i>EWSR1</i> or <i>PLAG1</i> gene rearrangement.</p> <p>Maximum one test per lifetime</p> <p>Fee: \$xxx.xx Benefit: 75% = \$xxx.xx 85% = \$xxx.xx.</p>
<p>XXXXX-19</p> <p>Analysis of tumour tissue from a patient with clinical or laboratory evidence of renal cell carcinoma, as requested by a specialist or consultant physician, for the characterisation of one or more of the following gene rearrangements:</p> <ul style="list-style-type: none"> <li>c) <i>TFE3</i>; or</li> <li>d) <i>TFEB</i>.</li> </ul> <p>Maximum one test per lifetime</p> <p>Fee: \$xxx.xx Benefit: 75% = \$xxx.xx 85% = \$xxx.xx.</p>

## 7. Summary of public consultation feedback/consumer Issues

There was no external consultation sought for this application beyond the stakeholders attending the “Pathology Pilot Meeting” held at the RCPA on 16 May 2019.

## 8. Proposed intervention’s place in clinical management

The clinical utility of each test, and the place of each in contemporary Australian practice, were discussed and confirmed by the pathology and specialist at the Pathology Pilot Meeting. There are no tests proposed in the application with variations of unknown significance.

The assessment of ploidy status in the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) guideline utilises a standard methodology by fluorescent in situ hybridisation.



The current World Health Organization (WHO) classification of tumours of the urinary system and male genital organs includes TFE3 & TFEB rearrangement for the assessment of renal carcinoma<sup>1</sup>. By virtue of the entry of these tests in the WHO Guideline it was accepted that they provide sufficient demonstration of diagnostic performance, clinical validity and/or clinical utility.

The current WHO classification of head and neck tumours includes the subtypes of salivary tumours of mucoepidermoid carcinoma, analogue secretory carcinoma and hyalinising clear cell carcinoma<sup>2</sup>.

## 9. Comparator

The comparator for this application is “no genetic testing” for each of the genetic abnormalities described.

## 10. Comparative safety

For this application, there was no assessment of the comparative safety of testing. The application stated that for each investigation “(t)he proposed test involves equivalent safety issues to current tissue pathology investigations”.

### *Test adverse events*

Each of the proposed tests is to be performed on a tissue specimen, the exact nature depending on the disease type, which would already have been taken for the purposes of tumour morphological assessment. It is not expected that there would be adverse events directly associated with testing. However, if a sample is insufficient or of too poor quality, a second sample may be required to provide results.

The main downstream effect of the proposed test is to provide a definitive diagnosis for the patient and thus inform subsequent patient interactions and management. Where the test results in a diagnosis associated with a poor prognosis, the test result is expected to be delivered by a specialist physician who can counsel the patient appropriately.

### *Adverse events from change in management*

Among the proposed tests, diagnostic and predictive value for a change in patient treatment is anticipated where patients are diagnosed with a NUT midline carcinoma<sup>3</sup>.

There are no adverse consequences anticipated from the use of any of the proposed tests. None of the proposed tests are considered experimental, nor is their use anticipated to directly lead to access to therapies which are not currently approved for use in Australia.

## 11. Comparative effectiveness

### *Direct effectiveness*

According to the supportive WHO guidance documents and published literature, each of the tests is used for diagnostic purposes. In addition, the tests for ploidy status in hydatidiform mole, *NUTM1* translocation in midline carcinomas, *ETV6-NTRK3* in breast and salivary gland tumours, and *MALM2* and *EWSR1* in salivary tumours, have prognostic value.

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<sup>1</sup> Moch H., Humphrey P.A., Ulbright T.M., Reuter V.E. WHO Classification of Tumours of the Urinary System and Male Genital Organs. 4th ed. IARC Press; Lyon, France: 2016.

<sup>2</sup> Adel K El-Naggar, John KC Chan, Jennifer R Grandis, Takashi Takata, Pieter J Slootweg IARC WHO Classification of Head and Neck Tumours, No 9. Fourth Edition. IARC Press; Lyon, France: 2017.

<sup>3</sup> Chau, N. et al. Intensive treatment and survival outcomes in NUT midline carcinoma of the head and neck. Cancer 2016. DOI: 10.1002/cncr.30242

The tests for *TFE3* and *TFEB* rearrangement have diagnostic and prognostic value in the assessment of patients with renal carcinoma.

### **Clinical claim**

The application stated that the overall clinical claim was for superiority over not testing for each of the genetic defects described.

## **12. Economic evaluation**

Based on MSAC Executive advice for related application 1526 and 1527, the Department proposed that a full economic evaluation was not warranted for this application.

## **13. Financial/budgetary impacts**

An epidemiological approach has been used to estimate the financial implications of listing each of the proposed tests on the MBS (see Table 3).

There is no Australian registry for hydatidiform molar pregnancy; the incidence varies according to maternal age from 1:200 to 1:1000 pregnancies with an estimated incidence of 500 cases in Australia per year.<sup>4</sup> The Royal Australasian and New Zealand College of Obstetricians and Gynaecologists recommend testing ploidy status at the initial diagnosis of hydatidiform mole.

The proposed test *FOXL2* 402 C>G is performed in patients with histologically confirmed granulosa cell tumour. Based on complete data for 2015 (subsequent years are currently incomplete) the Australian institute of Health and Welfare estimated the incidence of ovarian cancer to be 905 cases.<sup>5</sup> Granulosa cell tumour of the ovary represents 3-5% of all ovarian tumours (i.e. maximally 45 cases per year).<sup>6</sup>

The incidence of salivary gland tumour is estimated to be 6% of all head and neck tumours.<sup>7</sup> Based on complete data for 2015 (subsequent years are currently incomplete) the Australian Institute of Health and Welfare estimate the incidence of all head and neck cancer to be 4633 cases.<sup>2</sup> Mucoepidermoid cancer of the salivary gland accounts for approximately 50 % of all cases. Hyalinising clear cell carcinoma and analogue secretory carcinoma of the salivary gland account for approximately 1% of all cases, each.

The pathognomonic feature of NUT midline carcinoma is the presence of the specific translocation between the *NUT* gene on chromosome 15q14 and other genes.<sup>8</sup> The recognised difficulty in identifying the true incidence of NUT midline is the lack of pathogenomic histological features of the condition that require further diagnostic testing, resulting in a slow increase in the number of cases identified over time. The number of reported cases of NUT midline carcinoma in an international registry is less than 100, worldwide.<sup>2</sup> Conservatively, the number of patients proposed to be tested in Australia is estimated at 150 by the applicant. Based on complete data for 2015, the AIHW estimate the incidence of all breast cancers to be 17004 cases.<sup>2</sup> The proportion of all breast cancers that have a secretory phenotype is 0.02%.<sup>9</sup>

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<sup>4</sup> Royal Australasian and New Zealand College of Obstetricians and Gynaecologists. Statement for the management of gestational trophoblastic disease. March 2017

<sup>5</sup> <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/summary>

<sup>6</sup> Farkkila, A. et al. Pathogenesis and treatment of adult-type granulosa cell tumour of the ovary. *Annals of Medicine*.2017; 49(5): 435-447

<sup>7</sup> Eveson, J. Salivary tumours. *Periodontology* 2000. 2011;57: 150-159.

<sup>8</sup> Pass, H. Ball, D & Scagliotti, G. *Thoracic Oncology* (second edition) 2018. Elsevier. ISBN978-0-323-52357-8

<sup>9</sup> Jacob, J et al. Rare breast cancer: 246 invasive secretory carcinomas from the National Cancer Data Base. *Journal of surgical Oncology*. 2016; 113(7): 721-5

Based on complete data, the AIHW estimate the incidence of renal cell carcinoma in 2015 to be 3882 cases.<sup>2</sup> The estimated proportion of all renal cell carcinomas that are *TFE3* rearranged, which confers a worse prognosis, is 1%.<sup>10</sup> However, the applicant states that approximately 10% of the incident population would require the proposed test.

**Table 3: Estimated disease incidence and number of tests to be performed annually**

Genetic test(s)	Tumour type	Estimated number of new cases per year (n)	Estimated number of tests to be performed per year (n)
Ploidy status Parental status	Hydatidiform mole	500	500
<i>FOXL2</i> 402 C>G	Granulosa ovarian	45	45
<i>NUTM1</i> 15q14	Midline carcinomas	150	150
<i>MAML2</i>	Mucoepidermoid salivary gland carcinoma	139	139
<i>EWSR1</i> or <i>PLAG1</i>	Hyalinising clear cell salivary gland carcinoma	46	46
<i>ETV6-NTRK</i>	Secretory breast cancer	3	3
	Analogue secretory salivary gland carcinoma	46	46
<i>TFE3, TFEB</i>	Renal cell carcinoma	3882	388

*The number of balloon enteroscopy procedures performed in Australia is projected to increase to 604 in 2017/18. Based on these figures, the estimated increase of MBS expenditure for balloon enteroscopy over 4 years will be less than \$100,000.*

<sup>10</sup> Sukov, W et al. *TFE3* rearrangements in adult renal cell carcinoma: clinical and pathologic features with outcome in a large series of consecutively treated patients. *American Journal of Surgical Pathology*. 2012; 36(5): 663-670

## 14. Key issues from ESC for MSAC

Key issue	Departmental advice to MSAC
Clinical claim reasonable	The current statement on the management of gestational trophoblastic disease by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) serves as the standard of care for Australian patients, which includes the assessment of ploidy status at initial diagnosis.  Given the very low incidence of the other tumour types in this application, the relevant tests are described in published literature and not in clinical practice guidelines.
Testing methodology	The MBS item descriptor in the application only described the methodology for assessing ploidy status in hydatidiform mole
Determination of diagnostic performance, clinical validity and clinical utility	The Department and applicant had agreed an approach to the determination of clinical utilities for each of the proposed tests, based on a triage assessment developed prior to, and discussed at, the Pathology Pilot Meeting.  The entry of some of the requested tests in the current World Health Organization classification of urinary tract tumours and classification of head and neck tumours was accepted to provide sufficient demonstration of their diagnostic performance, and also its clinical validity and/or clinical utility. Further assessment of these aspects was not sought for this application for each proposed test due to the extremely rare incidence of each tumour type.
Limitations on number of tests	Each of the tests described are proposed to be performed once per patient lifetime.
Economic evaluation and financial analysis	Given the relatively small patient populations of each disease type who require each genetic test, the estimated fee for each service involving an individual test, and the estimated annual total cost of funding all the tests in the application, it was proposed by MSAC Executive that a full HTA assessment would not be required prior to consideration of funding by MSAC.
Uncertainty with financial inputs	Given the estimated very low incidence of the each of the genetically defined tumour subtypes described, and a lack of Australian registry data, there may be variability in the number of patients who require testing. However, based on available data, the number of tests per year is not expected to be substantially larger than described.

The purpose of the application is to seek Medicare Benefits Schedule (MBS) listing of somatic gene testing in the context of patients with hydatidiform mole, granulosa cell tumour of the ovary, midline squamous cell carcinoma, salivary gland carcinoma, secretory carcinoma of the breast and renal cell carcinoma. Each of the proposed tests was determined by the applicant and the Department as having clinical utility.

The Royal Australasian and New Zealand College of Obstetricians and Gynaecologists recommend the assessment of ploidy status at initial diagnosis of patients with hydatidiform mole. Due to their rare incidence, the remaining tests are described only in published literature and not in clinical practice guidelines.

The application states that each of the proposed tests offers superior effectiveness and non-inferior safety compared with no testing.

Is there need for further assessment of diagnostic performance for all the proposed tests?

Is there need for further assessment of clinical validity and utility?

Based on the precedent set from applications 1526 and 1527, is the financial analysis presented in Section 12 below sufficiently accurate to be relied on to inform decision making?

A further discussion on the three applications to finalise the item descriptor wording was held at the MSAC Executive meeting on 16 August 2019. It was agreed that the item for hydatidiform mole requires further specialist pathologist input prior to approval. All other items were considered appropriate for approval. It was agreed that there should be two separate items for testing of *ETV6-NTRK3* in secretory carcinoma of the breast and secretory carcinoma of the salivary gland.

**15. Other significant factors**

Nil.

**16. Applicant's comments on MSAC's Public Summary Document**

The College would like to take this opportunity to thank the Department and the MSAC for their assistance in moving this application forward to a successful outcome that will deliver great benefits for a small group of vulnerable patients. The College is seeking clarification on a number of issues, which may be crucial in the drafting of the item number descriptors.

**17. Further information on MSAC**

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)