

MSAC application 1790

POLE genotyping for the molecular classification of endometrial cancer

Application for MBS eligible service or health technology

HPP Application number:

HPP200178

Application title:

POLE genotyping for the molecular classification of endometrial cancer

Submitting organisation:

THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA

Submitting organisation ABN:

52000173231

Application description

Succinct description of the medical condition/s:

Although the incidence of endometrial carcinoma (EC) is relatively low in Australia compared to other more common cancers, it is the 5th most common cancer in females and the most common gynaecological cancer (95% of diagnosed uterine cancers are endometrial cancers, arising from the inner lining of the uterus). Incidence of EC has increased over time, and although 5-year survival rates are good (84%), it is still associated with significant morbidity and mortality (1, 2).

Succinct description of the service or health technology:

Molecular characterisation of endometrial malignancies as per diagnostic criteria within the WHO Classification of Female Genital Tumours to establish pathologic risk stratification to guide treatment decisions. EC should only be classified as POLEmut, when pathogenic variants of POLE are identified in the exonuclease domain of the POLE gene. The technique used for the mutational analysis of POLE (exons 9, 11, 13, 14) described in the MBS item descriptor should remain agnostic as it is dependent on laboratory expertise and resources. Although Sanger sequencing, polymerase chain reaction (PCR) or next-generation approaches (6, 9) can be used, NGS would be the preferred (gold standard) technique based on sensitivity and lower limit of detection. Although NGS is more expensive, it is cost-effective compared to other methods and would future-proof the item to detect uncommon pathogenic POLE.

Application contact details

Are you the applicant, or are you a consultant or lobbyist acting on behalf of the applicant?

Applicant

Are you applying on behalf of an organisation, or as an individual?

Organisation

Applicant organisation name:

THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA

Application details

Does the implementation of your service or health technology rely on a new listing on the Pharmaceutical Benefits Scheme (PBS) and/or the Prescribed List?

No

Is the application for a new service or health technology, or an amendment to an existing listed service or health technology?

New

Relevant MBS items

Please select any relevant MBS items.

| MBS item number | Selected reason type |
|-----------------|----------------------|
|-----------------|----------------------|

What is the type of service or health technology?

Investigative

Please select the type of investigative health technology:

Molecular diagnostic tests

Please select the type of molecular diagnostics health technology:

Single gene assay

PICO sets

Application PICO sets:

Women with confirmed endometrial cancer undergoing POLE mutational analysis

State the purpose(s) of the health technology for this PICO set and provide a rationale:

Purpose category:

Diagnosis / sub-classification

Purpose description:

To establish a diagnosis or disease (sub)classification in symptomatic or affected patients

Population

Describe the population in which the proposed health technology is intended to be used:

Uterine cancer is the most common gynaecological cancer diagnosed in Australian women, with 90-95% of these cancers being endometrial cancers, a malignancy arising from the inner epithelial lining of the uterus (Figure 1) (27, 28).

Most patients diagnosed with endometrial cancer are postmenopausal with a median age at diagnosis of 60 years; however, rates of EC are steadily increasing over time, especially in younger, premenopausal women, which may be related to an increase in risk factors including high and rising rates of obesity, and shifts in reproductive trends, including women having fewer children and delaying childbirth until later in life (29). In 2023, the estimated number of women diagnosed with EC in Australia would have been 2,986, equivalent to an age-standardised rate of 21.8 per 100,000 females. Rates of EC increase steadily in women aged >35 years, peaking in the 65–75-year age bracket (Figure 2). Rates of survival are generally extremely good in women with EC, with 84.4% of women surviving 5-years after being diagnosed with EC (95% CI [83.6, 85.2%]) (1, 2).

Traditionally, endometrial carcinomas are classified according to histopathological subtypes (Type I and II) and tumour grade (I-III), with Type I (favourable prognosis) primarily composed of grade I or grade II endometrioid adenocarcinomas, and Type II (unfavourable prognosis) including grade III endometrioid adenocarcinomas, serous clear cell, undifferentiated and carcinosarcomas (29, 30). Although histological classification is useful in determining further surgical and adjuvant

therapy, decision-making can be complicated by an overlap between the subtype and grade of a tumour as well as interobserver variability in classification. Incorporating molecular classification into the standard histologic classification of EC will precisely define subtypes and guide therapeutic decision-making (29). A diagnostic algorithm may include the use of three immunohistochemical markers (p53, MSH6 and PMS2) as well as mutational analysis of the POLE gene (7). Approximately 7-10% of all ECs have a POLE mutation, characterised by microsatellite stability and a high burden of somatic mutations in the polymerase epsilon DNA (POLE) exonuclease domains (31). Patients who are POLEmut have an excellent prognosis, with comparable recurrence-free and overall survival rates regardless of post-surgical adjuvant therapy (14). Therefore, de-escalation to no adjuvant treatment is recommended for patients with low-risk, stage I-II POLEmut endometrial carcinoma (5, 7, 8). It is; however, recommended that all women with EC undergo risk stratification with POLE mutational analysis regardless of histological classification (11, 32).

Select the most applicable Medical condition terminology (SNOMED CT):

Endometrial carcinoma

Intervention

Name of the proposed health technology:

Molecular characterisation of endometrial malignancies as per WHO diagnostic criteria of Female Genital Tumours in order to establish pathologic risk stratification that can be used to guide treatment decisions. EC should only be classified as POLEmut, when pathogenic variants of POLE are identified in the exonuclease domain of the POLE gene (exons 9, 11, 13, 14) using an agnostic technique.

Comparator

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

The nominated comparator is no POLE mutational analysis. Post-surgery, the hysterectomy specimen would undergo MMR, p53 and ER immunohistochemistry, but, in the absence of POLE mutational analysis, de-escalation or escalation of treatment according to mutational analysis would not occur. Patients would be

treated on the basis of their histological findings alone, which could include observation, radiation, chemotherapy or both.

Outcomes

Outcome description – please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

Safety Outcomes:

Adverse events (AEs) related to POLE testing

AEs from change in patient management (adjuvant therapy verses no adjuvant therapy)

AEs from treatment (if given)

Clinical Effectiveness Outcomes:

Direct evidence:

Change in patient health outcomes: mortality, morbidity, quality of life: Clinical utility: change in patient management/treatment resulting in change in patient outcomes: mortality, morbidity, quality of life: comparing patients who POLE genotyping versus those who did not receive POLE genotyping

Indirect evidence

Clinical utility: change in patient management/treatment resulting in change in patient outcomes: mortality, morbidity, quality of life

Clinical validity: prognostic value: assessment of diagnostic/test accuracy: sensitivity, specificity, number of false positives, number of false negatives, number of inconclusive results

Cost-effectiveness outcomes:

Cost per patient with a POLE variant identified.

Cost per patient avoiding adjuvant therapy

Cost per quality-adjusted life year (QALY) gained.

Health system resources:

Cost of molecular testing vs. saving costs of adjuvant therapy

Total Australian Government healthcare costs

Proposed MBS items

Proposed item:

AAAAA

MBS item number

Category number:

PATHOLOGY SERVICES

Category description:

GENETICS

Proposed item descriptor:

Characterisation of variants in the exonuclease domain (targeting exons 9, 11 13 and 14 as a minimum) of the POLE gene, requested by a specialist or consultant physician in a patient diagnosed with endometrial carcinoma.

Applicable once per lifetime

Proposed MBS fee:

\$550.00

Indicate the overall cost per patient of providing the proposed health technology:

\$550.00

Please specify any anticipated out of pocket expenses:

\$0.00

Provide any further details and explain:

Nil

How is the technology / service funded at present? (For example: research funding; State-based funding; self-funded by patients; no funding or payments):

Testing is currently funded by state-based funding (if offered) or as an out-of-pocket payment by those informed patients who can afford to pay.

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)?

Superior

Please state what the overall claim is, and provide a rationale:

Given that there is no current MBS item number that covers this testing, this testing is either currently being performed at cost to the referring pathology provider/patient or not being performed. Public funding of these genetic tests would align Australian clinical practice with the established clinical practice guidelines and diagnostic standard of care as stipulated by the revision of the WHO classification of female genital tumours. Access to genetic testing will allow more patients to have a more accurate assessment of the risk of recurrence and the need for adjuvant therapy, resulting in better patient management and improved outcomes.

At its August 2019 meeting, MSAC supported genetic tumour testing applications 1526, 1527 and 1528. The PSDs for these applications note that by virtue of their place in the WHO guidelines, the proposed genetic tests have documented clinical utility in these diseases. MSAC confirmed that it accepts the entry of each test into the WHO guidelines as sufficient demonstration of its diagnostic performance, clinical validity (prognostic value), and clinical utility (resulting in changes to subsequent clinical management), therefore the precedent has been established for MSAC accepting such claims based on WHO guidelines.

Recommendations of adjuvant therapy (chemotherapy or radiation therapy) are based on the individual patient's risk of disease recurrence using clinicopathologic factors such as age, stage, grade, lymphovascular invasion, and the presence of molecular variants in, amongst others, the POLE gene (21). By implementing POLE testing in routine diagnostics and omitting adjuvant therapy in EC patients with low-intermediate risk features, overtreatment of a substantial group of patients would be avoided, with a clear impact on the patient's quality of life (19).

Estimated utilisation

Estimate the prevalence and/or incidence of the proposed population:

Some data sources report rates of uterine rather than endometrial cancer, therefore it should be noted that 95% of diagnosed uterine cancers are endometrial cancers, arising from the inner lining of the uterus (27). Although incident rates of uterine cancer are relatively low compared to other cancers, in 2023 it remains the 5th most common cancer in females. Rates of EC have been reported to be steadily increasing over time, which may be related to an increase in risk factors including high and rising rates of obesity, and shifts in reproductive trends, including women having fewer children and delaying childbirth until later in life. In 2023, it is estimated that 2,986 women would be diagnosed with EC in Australia, equivalent to an age-standardised rate of 21.8 per 100,000 females. Rates of EC increase steadily in

women aged >35 years, peaking in the 65–75-year age bracket (Figure 5). Rates of survival are extremely good in women with EC, with 84.4% or women surviving 5-years after being diagnosed with EC (95% CI [83.6, 85.2%]) (1, 2).

Approximately 7-10% of EC cases are POLEmut (excellent prognosis), with 28% having microsatellite instability (intermediate prognosis), 39% low copy-number (good prognosis) and 26% with high copy number (worst prognosis) (6, 33).

Provide the percentage uptake of the proposed health technology by the proposed population:

Year 1 estimated uptake (%):

100

Year 2 estimated uptake (%):

100

Year 3 estimated uptake (%):

100

Year 4 estimated uptake (%):

100

Estimate the number of patients who will utilise the proposed technology for the first full year:

3056

Optionally, provide details:

All women with EC confirmed after surgery should undergo POLE mutational analysis. This would equate to approximately 3,056 women being tested in the first year of the proposed medical service. Over the past 3-years in Australia, the number of newly diagnosed endometrial cancer cases has increased by an average of 2.36 percent each year (2).

Therefore:

2023 = 2,986

Expected 2024 = 3,056

Expected 2025 = 3,128

Expected 2026 = 3,202

Will the technology be needed more than once per patient?

No, once only

Consultation

List all entities that are relevant to the proposed service / health technology. The list can include professional bodies / organisations who provide, request, may be impacted by the service/health technology; sponsor(s) and / or manufacturer(s) who produce similar products; patient and consumer advocacy organisations or individuals relevant to the proposed service/health technology.

Entities who provide the health technology/service

Australian Pathology

Public Pathology Australia

Entities who request the health technology/service

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists

Australia New Zealand Gynaecological Oncology Group

Australian Society of Gynaecologic Oncologists (ASGO)

RANZCR Faculty of Radiation Oncology

Entities relevant to the proposed service/health technology

CounterPart

Australia New Zealand Gynaecological Oncology Group (ANZGOG)

Lynch Syndrome Australia

Regulatory information

Would the proposed health technology involve the use of a medical device, in-vitro diagnostic test, radioactive tracer or any other type of therapeutic good?

No