Population

Describe the population in which the proposed health technology is intended to be used:
Cholangiocarcinoma (CCA) is a rare cancer that encompasses all tumours originating from the epithelium of the bile duct. Bile ducts are a group of thin tubes that carry bile (a digestive fluid) from the liver and gallbladder into the intestines (Rare Cancers Australia 2022). CCA can be categorised into two types (Brindley, Bachini et al. 2021):

- intrahepatic CCA (iCCA) – this type of cancer forms in the bile ducts inside the liver.
- extrahepatic CCA (eCCA) – this type of cancer forms in the bile ducts outside the liver. Extrahepatic cancer can be further distinguished by which region the cancer can form:
    - perihilar CCA: this type of cancer that is found in the hilum region the area where the right and left bile ducts exit the liver and join to form the common hepatic duct.
    - distal CCA: this type of cancer is found in the distal region and is made up of common bile duct which passes through the pancreas and ends in the small intestine.

Although CCA is an uncommon disease, the global incidence of CCA has been rising in recent years (Khan, Emadossadaty et al. 2012, Rizvi, Khan et al. 2018) owing to an increase in the underlying risk factors for the disease. Globally, the incidence of CCA is estimated to be between 0.3-6 cases per 100,000 people (Banales, Marin et al. 2020). The true incidence of iCCA and eCCA is unclear, owing to misclassification between the two types in many national databases (Khan, Tavolari et al. 2019). It is estimated that ~1,161 new cases of CCA were diagnosed in Australia in 2022, based on data from the Australian Institute of Health and Welfare (AIHW) (Australian Institute of Health and Welfare 2022).

Isocitrate dehydrogenases (IDH) are essential metabolic enzymes for cellular respiration in the tricarboxylic acid cycle (Boscoe, Rolland et al. 2019). A mutation in the *IDH* gene leads to the increased conversion of α-KG to D-2-hydroxyglutarate (D-2HG), which acts as an oncometabolite, promoting tumour proliferation and metastasis development through several pathways, such as DNA methylation and activation of vascular endothelial growth factors (VEGFs) (Salati, Caputo et al. 2020). The two main subtypes of *IDH* are *IDH*1 and *IDH*2.

In the early stages of CCA, patients are often asymptomatic, hence they often present with advanced disease (Blechacz, Komuta et al. 2011, Brindley, Bachini et al. 2021). Symptomatic patients will vary in clinical presentation depending on the location of the tumour and growth pattern (Blechacz, Komuta et al. 2011). Patients diagnosed with iCCA often present asymptomatically during early stages of disease but will later develop symptoms such as abdominal pain or uncommonly, jaundice during progression into advanced stage. Patients diagnosed with eCCA typically present with painless jaundice owing to the underlying biliary obstruction (Brindley, Bachini et al. 2021). The general symptoms of CCA are consistent with the clinical presentation for biliary obstruction i.e. jaundice, pale stool, dark urine and pruritus. Other common symptoms can include, abdominal pain, malaise, weight loss, fatigue, fever, cachexia and night sweats (Blechacz 2017, Brindley, Bachini et al. 2021).

CCA is among the most challenging cancers to treat and is often associated with poor prognosis both in the early and advanced stages due to its silent clinical character. The 5-year survival of

CCA is around 2% if diagnosed in the advanced stage (Cancer.Net 2022). The current treatment landscape for CCA is generalised to broad biliary tract cancer, with limited second-line treatment options available. Hence, there is a significant clinical need for new targeted treatments. Although *IDH1* mutations have been found in CCA, there is no standard genetic screening tests currently available in Australia.

Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed health technology, describing how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the technology:

Management of CCA patients in the lead up to genetic testing of tumour tissue
Following initial symptomatic presentation to a general practitioner (GP), investigative tests are performed including physical examination are conducted to assess the presence of jaundice (assessment of hepatomegaly, splenomegaly, ascites, abdominal collateral circulation, palmar erythema or spider naevi, telangiectasia, gynecomastia, parotid hypertrophy or Dupuytren's contracture) (Forner, Vidili et al. 2019). Following physical examination, laboratory tests are conducted i.e. blood tests with full liver function are performed before proceeding with imaging for further investigation (Forner, Vidili et al. 2019, Shin, Moon et al. 2023). If the patient is suspected or diagnosed with CCA, a referral to a specialist is provided, with primary care accompanied in a multidisciplinary setting. Specialist diagnostic tests are conducted to confirm stage, type, and histology. Tumour biopsy is performed to collect samples, which is done through a variety of techniques such as fine need biopsy and are generally performed by interventional radiologists, surgical oncologists or pathologists.

Characteristics of patients with advanced CCA positive for IDH1 mutation
A diagnosis of CCA is rare and often carries a poor prognosis as it is generally diagnosed in the advanced stages (Clements, Eliahoo et al. 2020, Brindley, Bachini et al. 2021). CCA is more commonly diagnosed in men than women, with an average age of diagnosis between 60-70 years (Ioffe, Phull et al. 2021). CCA typically presents late, with non-specific symptoms and when coupled with the lack of knowledge surrounding potential risk factors, an early diagnosis for CCA is uncommon (Clements, Eliahoo et al. 2020). The overall 5-year survival for extrahepatic CCA is 10%, while the 5-year survival for intrahepatic CCA is 9% (Cancer.Net 2022). However, due to its silent clinical characteristics CCA is categorised as one of the most fatal cancers with a 5-year survival rate of approximately 2% if diagnosed in the advanced stage (Cancer.Net 2022).

CCA is heterogeneous and is classified according to the primary anatomic subtypes: extrahepatic CCA or intrahepatic CCA. Extrahepatic CCA forms in the bile ducts outside the liver and is made up of the hilum region (perihilar CCA) and the distal region (distal CCA). Intrahepatic CCA forms in the bile ducts inside the liver (Brindley, Bachini et al. 2021). Strong risk factors for both intrahepatic (iCCA) and extrahepatic CCA (eCCA) are cysts and stones in the bile ducts, cirrhosis, and hepatitis B and C viruses. Other risk factors include diabetes although this association is less strong. Global incidence of various risk factors is increasing, which may contribute to the rising incidence of CCA (Brindley, Bachini et al. 2021). Imaging for CCA is crucial in the detection and characterisation of CCA (Forner, Vidili et al. 2019). Overall, screening for CCA remains a challenge since the risk factors are poorly defined.

There are various genetic mutations that have been associated with CCA, such as *TP53*, *KRAS*, *IDH*1, *ARID1A*, *FGFR2* and *CDKN2A* (Carotenuto, Sacco et al. 2022). These genes are involved in vital cell survival and signalling pathways and are frequently harboured by CCA. CCA Patients harbouring an *IDH*1 mutation have also been associated with the pathogenesis of iCCA (Ahn and Bekaii-Saab 2016). Approximately 13% of iCCA carry an *IDH1* or *IDH2* mutation, whilst approximately 2-3% of eCCA patients carry these mutations (Carotenuto, Sacco et al. 2022). *IDH*1 mutations have been associated with poorly differentiated and clear-cell histology and have no association with histological grading in iCCA (Goyal, Govindan et al. 2015).

Patients eligible for the proposed medical service

The proposed medical service is a tumour tissue test to detect *IDH1* mutations in patients with locally advanced or metastatic CCA, to determine eligibility for ivosidenib under the PBS. It is proposed that patients will receive the genetic test upon diagnosis of CCA, as this will facilitate more timely access to targeted treatment upon disease progression.

The target population for ivosidenib treatment is patients with locally advanced or metastatic CCA who harbour an *IDH*1 mutation. Current guidelines for CCA patients recommend first-line combination chemotherapy; however patients who are refractory to treatment often resort to additional chemotherapy used ad hoc by clinicians (e.g. FOLFOX), best supportive care, or are encouraged to participate in clinical trials targeting genetic mutations such as IDH1 (Valle, Borbath et al. 2016, NCCN 2022, Vogel, Bridgewater et al. 2023).

There is hesitancy among clinicians to offer combination chemotherapies such as FOLFOX and FOLFIRI to patients with declining functional capacity and performance status due to the risk of adverse events such as infections. In the TOAZ-1 study (which compared first-line treatment with durvalumab or placebo in combination with gemcitabine and cisplatin), after first-line progression, 42.7% of patients received subsequent treatment with chemotherapy (Oh, Ruth He et al. 2022). Given that the inclusion criteria of clinical trials means that they tend to enrol patients with better performance status than patients in the routine practice, this proportion is expected to be at the upper end of the estimated use of FOLFOX in Australia.

Despite some use, evidence for the effectiveness of FOLFOX compared to best supportive care in treating advanced biliary tract cancers including CCA shows only limited benefit (median OS 6.2 months vs 5.3 months; HR = 0.69; p = 0.03) (Lamarca, Palmer et al. 2021). Evidence for FOLFIRI is limited to Phase II and retrospective studies, showing similar efficacy results to FOLFOX (eviQ 2022). As such, there is significant clinical need for additional treatment a treatment options in this population that can prolong overall survival and maintain quality of life. Furthermore, there is hesitancy among clinicians to offer combination chemotherapies such as FOLFOX and FOLFIRI to patients with declining functional capacity and performance status due to the risk of AEs such as infections, especially in the context of relatively moderate benefit.

Targeted *IDH1* therapy for CCA patients has been recommend by the National Comprehensive Cancer Network (NCCN) who emphasise the need for targeted molecular profiling for CCA. ESMO guidelines also recommend treatment with ivosidenib for CCA patients with an *IDH*1 mutation who have progressed after first-line systemic therapy (Vogel, Bridgewater et al. 2023). The ClarIDHy trial was a multicentre, randomised double blinded, placebo-controlled phase three trial that demonstrated the efficacy and safety of ivosidenib in *IDH*1 mutated second-line or third-line CCA patients (Abou-Alfa, Macarulla et al. 2020).

The testing population is broader than the drug population and will be a part of a routine gene marker testing, similar to the current testing for the *IDH*1 mutation testing in glial neoplasm (MBS item number 73372). Genetic biomarker testing at diagnosis would reduce tumour tissue attrition, thus minimising the risk of re-biopsy. Additionally, testing at diagnosis of CCA rather than after 1L progression will minimise delays in receiving 2L treatment. This is considered highly important in CCA, given the poor prognosis and short overall survival following 1L treatment. In Australian clinical practice, testing for *IDH*1 mutations will most likely be conducted using Pyrosequencing, Polymerase Chain Reaction (PCR) or Next Generation Sequencing (NGS), although the proposed MBS item will be method agnostic.

Provide a rationale for the specifics of the eligible population:
CCA is an aggressive malignancy and often carries a poor prognosis. The overall 5-year survival for extrahepatic CCA is 10%, while the 5-year survival for intrahepatic CCA is 9%, however for patients diagnosed in the metastatic stage, the survival drops to 2% at 5 years (Cancer.Net 2022). The current standard of care for locally advanced of metastatic CCA patients is broadly confined to best supportive care i.e. palliative care or combination systemic therapy (e.g. FOLFOX) as no specific treatments are available for this population group. Patients harbouring an *IDH*1 mutation may benefit from targeted treatment such as ivosidenib, which has been demonstrated to significantly improve PFS and OS in this population group, while maintaining quality of life.

It is proposed that all patients diagnosed with CCA will undergo testing for *IDH1* mutation, regardless of subtype classification of iCCA or eCCA. Although *IDH*1 mutations are more prevalent in iCCA, there is extensive misclassification between the two subtypes, and testing in eCCA is expected to ensure more equitable access to effective therapies. Given the limited treatment options for CCA, providing the proposed *IDH*1 test to all CCA patients would greatly advance the treatment options available for this patient population while promoting accessibility to potentially misclassified CCA patients.

Are there any prerequisite tests?
Yes

Are the prerequisite tests MBS funded?
Yes

Please provide details to fund the prerequisite tests:
Prior to tumour tissue testing for *IDH1* mutation, the patient must have histologically confirmed CCA. This test is currently funded under MBS items 72823/ 72824/ 72825/ 72826/ 72827 - Examination of complexity level 4 biopsy material with 1 or more tissue blocks, including specimen dissection, all tissue processing, staining, light microscopy and professional opinion.

It is not expected that there will be any changes in this prerequisite test as a result of the proposed test.

Intervention

Name of the proposed health technology:
Tumour tissue testing for *IDH*1 gene mutations*
TIBSOVO® (ivosidenib)

* Note this application does not nominate a specific test or test methodology.

Describe the key components and clinical steps involved in delivering the proposed health technology:
The proposed medical service is testing of tumour tissue for the presence of *IDH1* mutation in adult patients with locally advanced or metastatic CCA.

Molecular testing of IDH1 mutation using PCR or NGS
The key components and clinical steps involved in delivering *IDH*1 genetic testing in CCA patients are in line with those already in existence for *IDH*1 testing in glial neoplasm under MBS item 73372. It is understood that most Australian laboratories will utilise either pyrosequencing, PCR, Sanger sequencing or NGS technologies for molecular testing (RCPA 2023). The initial steps of extraction, isolation and quantification of tumour DNA from the biopsy specimens are the same for both NGS and PCR methods. The next key steps involved in molecular testing with NGS methods include preparation of sequencing libraries, enrichment of sequencing libraries for the genes of interest, sequencing of enriched libraries and analysis and reporting of test results. NGS-based gene panel tests can be customised to examine clinically important genes and is a first-choice technique in cancer-patient care. Although, access to NGS in a clinical setting may be limited as availability of this technique varies between states in Australia. The next key steps involved in molecular testing with PCR methods include amplification, post-PCR analysis and reporting of test results. There are no *IDH*1 diagnostic accuracy studies comparing PCR and NGS in CCA identified. The preferred time for testing *IDH*1 mutations is upon diagnosis of CCA or after progression on first-line treatment.

Tibsovo® (ivosidenib) treatment
Ivosidenib is a small selective, potent inhibitor of the mutant *IDH*1 enzyme. Mutant *IDH*1 converts alpha-ketoglutarate (α-KG) to 2-hydroxyglutarate (2-HG), and excess accumulation leads to downstream cellular activities such as impaired myeloid differentiation, increased proliferation of myeloblasts and reduced cellular differentiation (Crispo, Pietrafesa et al. 2020). Several trials have demonstrated a positive effect of *IDH*1 inhibition due to significant reductions in 2-HG levels and consequently inhibits tumour cell proliferation (Abou-Alfa, Macarulla et al. 2020, Fan, Mellinghoff et al. 2020)[1].

The recommended dose of ivosidenib is two 250 mg tablets (500 mg total) taken orally once daily. The duration of treatment is continued until disease progression or until treatment is no longer tolerated by the patient.

The TGA granted both priority and orphan designations for ivosidenib monotherapy for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an

[1] Current clinical trials assessing targeted IDH1 treatment (NCT02073994, NCT02989857, NCT04088188)

isocitrate dehydrogenase-1 (IDH1) mutation, who were previously treated by at least one prior line of systemic therapy.

For priority designation two of the four criteria warrant mention:
Criterion 3 – no therapeutic goods that are intended to treat, prevent or diagnose the condition are included in the Australian Register of Therapeutic Goods (ARTG) – The TGA advised - Patients who are clinically eligible will therefore receive 'off-label'/ unapproved intravenous chemotherapy regimens or seek participation in clinical trials. (Orphan designation – criterion 6 is the same as this priority criterion 3).

Criteria 4 – there is substantial evidence demonstrating that the medicine provides a major therapeutic advance. The TGA determined - Ivosidenib is an orally-dosed, well-tolerated, non-cytotoxic treatment with clinically meaningful benefit for patients with previously treated IDH1 mutant CCA.

Identify how the proposed technology achieves the intended patient outcomes:
Genomic profiling provides valuable insight on the disease prognosis, response to treatment and clinical management of CCA (Wakai, Nagahashi et al. 2020). There is evidence on the therapeutic impact of blocking the function of mutant *IDH*1 to reduce 2-HG levels, commonly detected in tumours and blood (Valle, Lamarca et al. 2017). By examining tumour biopsies collected from CCA patients, detection of an *IDH*1 mutation allows for targeted treatment with ivosidenib. The analysis of tumour tissue will be conducted using well established techniques such as PCR or NGS testing which will determine patient eligibility for treatment with ivosidenib.

If single gene testing of *IDH*1 is funded by the MBS, it will likely follow the existing MBS item 73372 for the identification of *IDH*1/2 pathological variant status for patients negative with glial neoplasm.

Key studies have highlighted the role of ivosidenib in CCA and demonstrated significant improvement in progression-free (Abou-Alfa, Macarulla et al. 2020, Zhu, Macarulla et al. 2021). The ClarIDHy trial was a multicentre, randomised double-blinded placebo-controlled trial that investigated the efficacy and safety of ivosidenib in IDH1 mutation in patients with locally advanced or metastatic CCA who had received at least one previous line of chemotherapy. 185 participants were enrolled in the study and randomised 2:1 to receive ivosidenib or placebo. 124 received 500 mg of ivosidenib daily per 28-day treatment cycle, and 61 received the placebo. Crossover to ivosidenib was allowed for participants who experienced disease progression in the placebo arm – resulting in 70% of patients in the placebo arm crossing over to receive ivosidenib. The results of the study found that treatment with ivosidenib was associated with significantly improved progression free survival (PFS) (median PFS for ivosidenib 2.7 months vs 1.4 months with placebo; HR 0·37; 95% CI 0·25–0·54; one-sided p<0·0001). Treatment with ivosidenib was associated with significantly improved OS after adjustment for treatment switching (median OS for ivosidenib 10.3 months vs 5.1 months with placebo; HR 0.49; 95% CI 0.34-0.7; one-sided p < 0.01). Overall, the study showed that in CCA patients with an *IDH1* mutation, ivosidenib significantly improves PFS and OS, while maintaining quality of life.

Testing patients with CCA for an *IDH*1 mutation is expected to lead to a change in the clinical management of these patients, as they will be able to receive targeted treatment with ivosidenib.

This change is expected to lead to a significant improvement in clinical outcomes, as demonstrated by the pivotal ClarIDHy trial.

Separately to this current application, Servier laboratories (Aust.) Pty. Ltd. is aware of an application in development by Rare Cancers Australia with the support of Omico for a panel of genetic tests, including IDH1 to determine eligibility to ivosidenib. Servier is supportive of this approach to clinical management and would welcome dialogue with the Department and other relevant stakeholders upon receipt of this application, as appropriate.

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components?
No

Explain whether it is essential to have this trademark component or whether there would be other components that would be suitable:
N/A

Are there any proposed limitations on the provision of the proposed health technology delivered to the patient (For example: accessibility, dosage, quantity, duration or frequency):
Yes

Provide details and explain:
Testing for *IDH*1 would be requested by primary physician or pathologist after the initial diagnosis of CCA. Each patient would only require one test to identify the presence of *IDH*1 mutations. It is unlikely a patient would require more than one *IDH*1 genetic test over their life.

If applicable, advise which health professionals will be needed to provide the proposed health technology:
NGS or PCR testing to identify *IDH*1 mutations should be conducted and the results be interpreted and reported by suitably qualified and trained molecular pathologists. Testing should be conducted in specialist laboratories holding the appropriate accreditation i.e. NATA accredited diagnostic testing procedure. The results should be interpreted and reported by suitably qualified and trained pathologists.

If applicable, advise whether delivery of the proposed health technology can be delegated to another health professional:
N/A

If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:
Testing to identify *IDH*1 mutation in patients with locally-advanced or metastatic CCA should be based on referral request from a specialist or consultant physician i.e. specialist oncologist.

Is there specific training or qualifications required to provide or deliver the proposed service, and/or any accreditation requirements to support delivery of the health technology?
Yes

Provide details and explain:
Testing for *IDH*1 mutations via NGS or PCR would be conducted by NATA-accredited laboratories and the results interpreted and reported by suitably qualified and trained pathologists.

Indicate the proposed setting(s) in which the proposed health technology will be delivered:
☐ Consulting rooms
☐ Day surgery centre
☐ Emergency Department
☐ Inpatient private hospital
☐ Inpatient public hospital
☒ Laboratory
☐ Outpatient clinic
☐ Patient's home
☐ Point of care testing
☐ Residential aged care facility
☐ Other (please specify)

Is the proposed health technology intended to be entirely rendered inside Australia?
Yes

Please provide additional details on the proposed health technology to be rendered outside of Australia:
N/A

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:

Test: As testing for *IDH*1 mutation is not currently funded for CCA patients, the comparator would be 'no testing'.

Treatment: The standard care for previously treated patients with locally advanced or metastatic CCA without an actionable genetic target (*IDH*1) is palliative care, or combination chemotherapy (FOLFOX, FOLFIRI). Based on data from the TOPAZ-1 study, up to 40% of patients are expected to receive second-line treatment with combination chemotherapy, while the majority of patients are currently expected to receive palliative care. Proportionally fewer patients are expected to receive third-line treatment with combination chemotherapy due to declining functional capacity and performance status and risk of adverse events such as infections. As such, no treatment/palliative care is expected to be the primary treatment comparator for this submission.

List any existing MBS item numbers that are relevant for the nominated comparators:
As the proposed comparator is no testing, there are no eligible MBS items.

Please provide a rationale for why this is a comparator:
Test: in line with current clinical practice, there is no genetic testing of tumour biopsy for CCA patients.

Treatment: The current management for previously treated patients with locally advanced or metastatic CCA is broadly generalised to biliary tract cancer. Patients are offered best supportive care, monotherapy, combination chemotherapy or are encouraged to participate in clinical trials. The majority of patients receive no further treatment beyond palliative care, while fewer than 40% may receive combination chemotherapy with either FOLFOX or FOLFIRI. Evidence to support the use of FOLFOX as a second-line treatment for advanced CCA comes from the ABC-06 study. In this study, patients who received treatment with FOLFOX had a modest improvement in OS compared to patients who received BSC (median 6.2 vs 5.3 months; HR, 0.69; 95% CI 0.50-0.97). FOLFIRI use in CCA is supported by limited Phase II and retrospective evidence (eviQ 2022). As such, the primary treatment comparator for this submission is no treatment/palliative care.

Pattern of substitution – Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator? (please select your response)

☐ None – used with the comparator
☐ Displaced – comparator will likely be used following the proposed technology in some patients
☐ Partial – in some cases, the proposed technology will replace the use of the comparator, but not in all cases
☒ Full – subjects who receive the proposed intervention will not receive the comparator

Please outline and explain the extent to which the current comparator is expected to be substituted:
The proposed health technology facilitates the access to targeted treatment with ivosidenib, and is expected to treat all locally advanced or metastatic CCA patients with an actionable *IDH1*mutation. Locally-advanced or metastatic CCA patients without an actionable *IDH1*mutation will continue receive best supportive care or standard combination chemotherapy.

Outcomes

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

☒ Health benefits
☐ Health harms
☐ Resources
☐ Value of knowing

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

As a result of a positive *IDH1* tumour tissue test, a change in clinical management would occur. Patients who harbour an *IDH1* mutation would be eligible to receive ivosidenib on the PBS, resulting in improved health outcomes such as increased progression-free survival, overall survival and maintenance of quality of life.

Test outcomes:

Trial based (evidentiary standard) analytical performance:

- Sensitivity
- Specificity
- Positivity predictive value (PPV)
- Negative predictive value (NPV)

Clinical utility of test:

Treatment effect modification of ivosidenib in patients with locally-advanced or metastatic CCA positive with an IDH1 mutation.

Other test-related considerations:

- Test turn-around time
- Estimated number of patients being tested
- Number needed to test
- Cost of testing per patient

Drug outcomes:

Safety outcomes:

Safety and tolerability of ivosidenib treatment assessed by adverse events, physical examinations, laboratory findings, and vital signs.

Clinical effectiveness outcomes:

- Progression-free survival (PFS)
- Overall survival (OS)
- Adverse events (AEs)
- Health-related quality of life (HRQoL)

The ClarIDHy trial (n=185) investigated the efficacy and safety of ivosidenib in IDH1 mutation in patients with locally advanced or metastatic CCA who had experienced disease progression on prior systemic therapy. The results of the study found that treatment with ivosidenib was associated with significantly improved progression-free survival (PFS) compared to placebo (median PFS for ivosidenib 2.7 months vs 1.4 months with placebo; HR HR 0·37; 95% CI 0·25–0·54; one-sided p<0·0001). Treatment with ivosidenib was associated with significantly improved OS after adjustment for treatment switching (median OS for ivosidenib 10.3 months vs 5.1 months with placebo; HR 0.49; 95% CI 0.34-0.7; one-sided p < 0.01). Overall, the study showed that in CCA patients with an IDH1 mutation, ivosidenib significantly improves PFS and OS, while maintaining quality of life.

Proposed MBS items

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

Currently, there is no government funding for diagnostic tests for *IDH1*mutations in CCA patients. Research funding is available through the MoST program. Testing is often self-funded by patients.

Please provide at least one proposed item with their descriptor and associated costs, for each population/Intervention: (please copy the below questions and complete for each proposed item)

Proposed item details

MBS item number (where used as a template for the proposed item)	MBS item 73372 is used as a template for the proposed item descriptor
Category number	Category 6
Category description	Pathology services
Proposed item descriptor	Analysis of tumour tissue, as requested by a specialist or consultant physician, that: • Is for a patient with histologically confirmed locally advanced or metastatic cholangiocarcinoma, • Is for the identification of IDH1 pathological variant status, • To determine eligibility for PBS-subsidised ivosidenib Applicable only once per lifetime
Proposed MBS fee	$340
Indicate the overall cost per patient of providing the proposed health technology	$340
Please specify any anticipated out of pocket expenses	N/A
Provide any further details and explain	

Algorithms

Preparation for using the health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology:
Adult patients are diagnosed with locally advanced or metastatic CCA. Following initial diagnosis, patients are referred by primary physician or specialist to test tumour tissue for *IDH1* mutation (testing is in-line with MBS item 73372 for *IDH1* testing in glial neoplasm). Positive *IDH1* mutation defines eligibility for targeted treatment with ivosidenib.

Is there any expectation that the clinical management algorithm *before* the health technology is used will change due to the introduction of the proposed health technology?
No

Describe and explain any differences in the clinical management algorithm prior to the use of the proposed health technology vs. the comparator health technology:
Patients will still require biopsy testing for diagnosis of CCA prior to receiving proposed healthcare technology or comparator health technology. Adult CCA patients who test positive for *IDH1* mutation will be eligible for treatment with ivosidenib. Patients that do not test positive for an *IDH1* mutation will continue to receive standard of care.

Use of the health technology

Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:
Healthcare resources that are used in conjunction with *IDH*1 testing include tumour biopsy (MBS item number 30694, endoscopic ultrasound (endoscopy with ultrasound imaging), with or without biopsy, with fine needle aspiration for the diagnosis of pancreatic, biliary or gastric submucosal tumours).

Explain what other healthcare resources are used in conjunction with the comparator health technology:
No additional healthcare resources are utilised as patients receiving standard of care would still receive a biopsy for diagnosis.

Describe and explain any differences in the healthcare resources used in conjunction with the proposed health technology vs. the comparator health technology:
Patients would still receive a biopsy as part of current standard of care. As such, there are no expected changes in adjunct medical resource utilisation.

Clinical management after the use of health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the proposed health technology:
It is anticipated most pathology laboratories will utilise NGS or PCR based gene panels to test for *IDH*1 mutation. It is proposed that *IDH*1 testing will occur at initial diagnosis of CCA, where the

presence of an *IDH*1 mutation will determine eligibility for treatment with ivosidenib upon progression on 1L systemic treatment.

Patients without an *IDH1* mutation will continue to receive standard of care.

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the <u>comparator health technology</u>:

In the absence of testing, patients will receive standard of care (i.e. palliative care, systemic chemotherapy with FOLFOX or FOLFIRI).

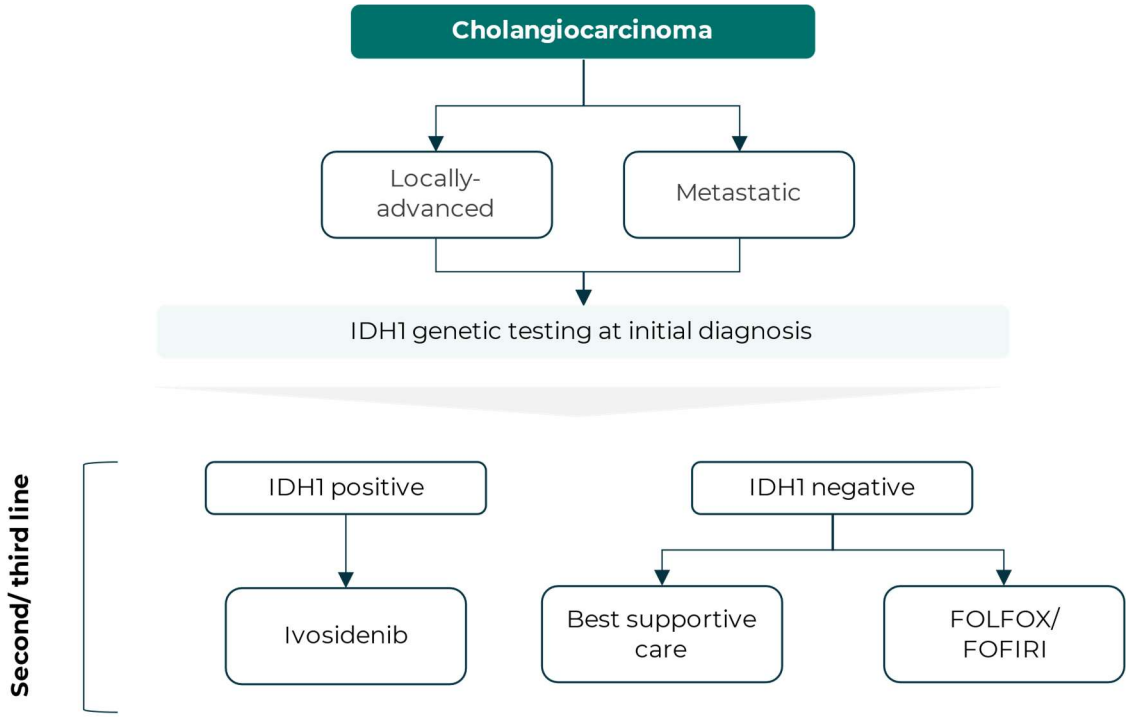
Describe and explain any differences in the healthcare resources used *after* the <u>proposed health technology</u> vs. the <u>comparator health technology</u>:

After the use of the proposed genetic testing, patients who test positive for *IDH*1 mutation will receive targeted treatment with ivosidenib through the PBS. Patients without a mutation will continue to receive standard of care.

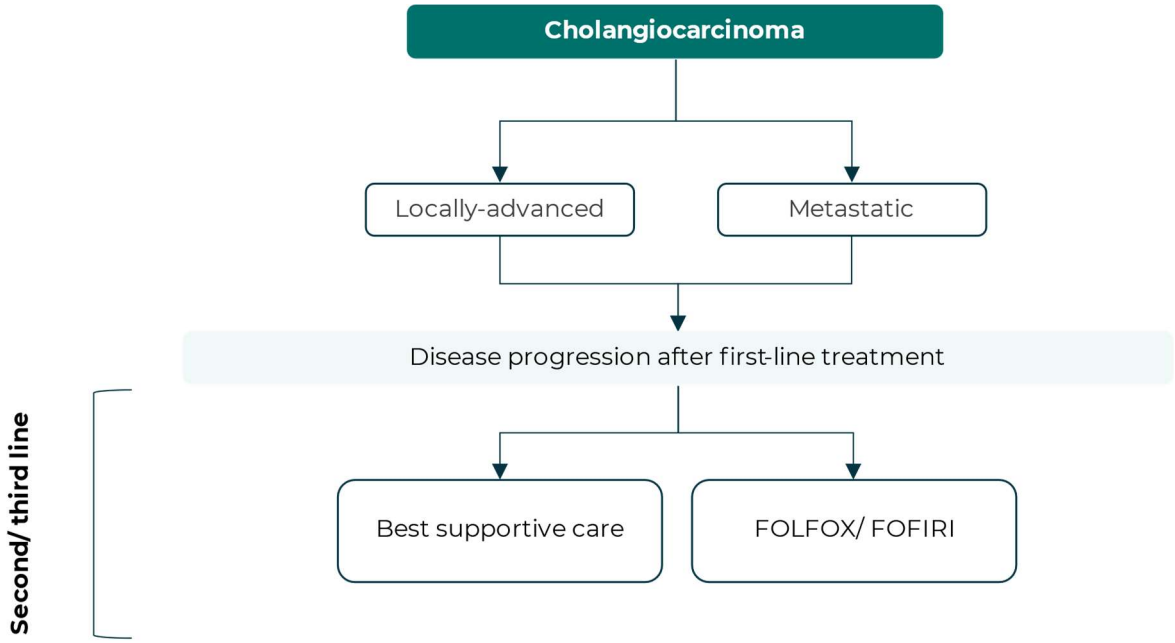
<u>Algorithms</u>

Insert diagrams demonstrating the clinical management algorithm with and without the proposed health technology:

<u>With proposed health technology:</u>



Without proposed health technology:



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)? (please select your response)

☒ Superior
☐ Non-inferior
☐ Inferior

Please state what the overall claim is, and provide a rationale:
Tumour tissue testing to determine IDH1 status, followed by targeted treatment with ivosidenib is superior to no genetic testing and untargeted care in patients with locally advanced or metastatic CCA.

In patients with locally advanced or metastatic CCA harbouring an IDH1 mutation , ivosidenib has been shown to significantly improve health outcomes compared to treatment with placebo (Abou-Alfa, Macarulla et al. 2020, Zhu, Macarulla et al. 2021). The ClarIDHy trial was an international, multicentre, randomised double-blinded placebo-controlled trial that investigated the efficacy and safety of ivosidenib in patients with IDH1 mutated locally advanced or metastatic CCA who had received at least one previous line of chemotherapy. 185 participants were assessed to be eligible and enrolled in the study and were randomly assigned (2:1) to receive 500 mg of either ivosidenib or matched placebo. The primary endpoint was progression-free survival, followed by the key secondary endpoints of overall survival, health-related quality of life and safety. Patients were allowed to cross-over into the intervention arm after disease progression in the placebo arm – resulting in 70% of patients in the placebo arm crossed over and receiving ivosidenib. The results of the study found that treatment with ivosidenib was associated with

significantly improved progression free survival (PFS) (median PFS for ivosidenib 2.7 months vs 1.4 months with placebo; HR: 0.37; 95% CI 0.25-0.54; one-sided p = <0.0001). For overall survival (OS), the study showed that treatment with ivosidenib was associated with significantly improved OS. After adjustment for treatment switching (median OS for ivosidenib 10.3 months vs 5.1 months with placebo (HR 0.49; 95% CI 0.34-0.70; one-sided p<0.01). Overall, ivosidenib was well tolerated with low rates of treatment discontinuation or dose reductions. Patients in the placebo arm experienced clinically meaningful reductions in physical functioning as measured by the EORTC QLQ-C30 physical function domain, while patients in the ivosidenib arm did not. The difference in the decline in physical function between the two groups was significant.

International regulatory bodies have recommended that patients with *IDH1* mutated CCA receive targeted treatment with ivosidenib. The NCCN recommended that treatment with ivosidenib as a subsequent line therapy for unresectable or metastatic CCA with an *IDH1* mutation following disease progression on 1L systemic treatment. The FDA have approved the use of ivosidenib for use in adult patients with previously treated, locally-advanced or metastatic CCA harbouring an *IDH1* mutation. The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has adopted a positive opinion and recommended granting a marketing authorization for ivosidenib tablets - for two indications: in combination with azacitidine, for the treatment of patients with newly diagnosed IDH1-mutated acute myeloid leukemia (AML) and not eligible for standard induction chemotherapy, as well as in previously treated, locally advanced or metastatic IDH1-mutated cholangiocarcinoma. In Australia, the TGA granted orphan drug and priority pathway designations for ivosidenib for previously treated, locally advanced or metastatic IDH1-mutated cholangiocarcinoma, TGA approval is expected b the end of April 2023.

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?
CCA is a rare and aggressive cancer with limited treatment options. Given the available evidence, patients with an actionable mutation may benefit from receiving a targeted treatment, rather than the current standard of care. Tumour tissue testing to determine eligibility for ivosidenib is expected to lead to a change in clinical management, as patients who harbour an *IDH1* mutation will receive targeted treatment.

Identify how the proposed technology achieves the intended patient outcomes:
Access to *IDH*1 gene testing improves health outcomes for patients by providing access to targeted treatments with proven efficacy and safety. Patients diagnosed with advanced CCA with an actionable mutation will have improved access to targeted treatments, improving their progression-free and overall survival while maintaining their quality of life.

For some people, compared with the comparator(s), does the test information result in:

A change in clinical management?	Yes
A change in health outcome?	Yes
Other benefits?	No

Please provide a rationale, and information on other benefits if relevant:

N/A

In terms of the immediate costs of the proposed technology (and immediate cost consequences, such as procedural costs, testing costs etc.), is the proposed technology claimed to be more costly, the same cost or less costly than the comparator?

☒ More costly
☐ Same cost
☐ Less costly

Provide a brief rationale for the claim:

- Cost of *IDH*1 testing is $340 per test (in-line with MBS item 73372, *IDH*1 testing in glioma)
- If patient is positive for *IDH*1, this will allow access to ivosidenib.

Summary of Evidence

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

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
1.	Phase III double-blinded, placebo controlled study	Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study	Assessed the efficacy and safety of ivosidenib (n=124) against placebo (n=61) in patients with IDH1-mutant CCA who had progressed on previous therapy. PFS improved in the ivosidenib arm compared to placebo ((median 2·7 months [95% CI 1·6–4·2] vs 1·4 months [1·4–1·6]. Safety results showed that ivosidenib was well tolerated.	https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(20)30157-1/fulltext	13 May 2020
	Phase III double-blinded, placebo controlled study	Final Overall Survival Efficacy Results of Ivosidenib for Patients With Advanced Cholangiocarcinoma With IDH1 Mutation The Phase 3 Randomized Clinical ClarIDHy Trial	Reported the OS results from the ClarIDHy trial. Median OS was 10.3 months (95%CI, 7.8-12.4 months) with ivosidenib vs 7.5 months (95%CI, 4.8-11.1 months) with placebo. ivosidenib was well tolerated and resulted in a favourable OS benefit vs placebo, despite a high crossover rate.	https://jamanetwork.com/journals/jamaoncology/fullarticle/2784216	23 September 2021 (Note: follow up analysis to initial publication)