

MSAC Application 1750

**Testing of tumour tissue to detect *IDH1* variants
in patients with cholangiocarcinoma to
determine eligibility for ivosidenib on the PBS**

PICO Confirmation

Summary of PICO/PPICO criteria to define question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Table 1 PICO for IDH1 p.R132X tier 1 variant testing in patients with locally advanced and metastatic cholangiocarcinoma (CCA)

Component	Description
Population	<p>Test: Adult patients with cholangiocarcinoma (CCA)</p> <p>Treatment: Patients with locally advanced or metastatic CCA who have disease progression following at least one line of chemotherapy</p>
Prior tests	Histological confirmation of CCA
Intervention	<p>Test: Tumour tissue testing for isocitrate dehydrogenase 1(<i>IDH1</i>) tier 1 variant status</p> <p>Treatment:</p> <ul style="list-style-type: none"> Ivosidenib as second or third-line treatment for locally advanced or metastatic CCAs in those with IDH1 p.R132X tier 1 variants Palliative care or second-line treatment: chemotherapy with 5-Fluorouracil (5-FU) and oxaliplatin (FOLFOX) or 5-FU plus irinotecan (FOLFIRI) in those without IDH1 p.R132X tier 1 variants
Comparators	<p>Test: No testing</p> <p>Treatment:</p> <ul style="list-style-type: none"> Primary comparator: palliative care Secondary comparator for second-line treatment: chemotherapy with 5-Fluorouracil (5-FU) and oxaliplatin (FOLFOX) or 5-FU plus irinotecan (FOLFIRI)
Clinical utility standard	Next-generation sequencing of the <i>IDH1</i> gene to identify tier 1 variant status at p.R132 of the IDH1 protein
Outcomes	<p>Test-related outcomes:</p> <p>Clinical utility of the test</p> <ul style="list-style-type: none"> Treatment effect modification for ivosidenib based on IDH1 p.R132X tier 1 variant status (predictive validity) <p>Other test-related considerations:</p> <ul style="list-style-type: none"> Number estimated to be tested Number needed to test (to identify one eligible case for ivosidenib) Test turn-around time Rate of re-biopsy (including test failure and inadequate sample rate) Safety of re-biopsy <p>Treatment-related outcomes:</p> <ul style="list-style-type: none"> Critical outcomes (GRADE): Progression-free survival (PFS) Overall survival (OS) Objective response rate (ORR) Important outcomes (GRADE): Time from randomisation to discontinuation or death (TDT) Health-related quality of life (HRQoL) Safety and tolerability: Treatment-emergent adverse events (TEAEs) Physical examination and laboratory findings <p>Health care system:</p> <ul style="list-style-type: none"> Cost of testing and associated re-biopsies per patient

Component	Description
	<ul style="list-style-type: none"> • Cost-effectiveness of testing and treatment • Financial implications
Assessment questions	<p>What is the safety, effectiveness, and cost-effectiveness of IDH1 p.R132X tier 1 variant testing and targeted treatment with ivosidenib versus no testing and palliative care or second-line chemotherapy in patients with locally advanced or metastatic CCA who have failed first- or second-line chemotherapy?</p> <p>Do results from IDH1 p.R132X tier 1 variant testing predict a treatment effect modification with ivosidenib?</p>

Purpose of application

The codependent application requested:

- Medicare Benefits Schedule (MBS) listing of isocitrate dehydrogenase 1 (*IDH1*) tier 1 variant testing (IDH1 p.R132X variants) for the determination of patient eligibility for treatment with ivosidenib (Tibsovo®); and
- Pharmaceutical Benefits Scheme (PBS) Authority Required listing of ivosidenib (Tibsovo®) for the treatment of patients diagnosed with locally advanced or metastatic cholangiocarcinomas (CCAs) who have an IDH1 p.R132X tier 1 variant and have disease progression after first or second-line treatment.

NOTE:

- An IDH1 p.R132X tier 1 variant refers to a variant with a change in the deoxyribonucleic acid (DNA) sequence at codon 132 of the *IDH1* gene, such that the resultant amino acid substitution leads to an abnormal ‘gain-of-function’ IDH1 protein (IDH1 p.R132X), as described in the section titled “Biological rationale for targeting IDH1 p.R132X tier 1 variants with ivosidenib.” This includes IDH1 p.R132C, p.R132G, p.R132H, p.R132L, and p.R132S, as well as any other amino acid substitution at p. R132 leading to a ‘gain of function’ oncogenic IDH1 protein.
- Throughout this document, when “*IDH1* testing” is used, it refers to genetic testing to identify a Tier 1 *IDH1* genetic variant which results in an “gain of function” amino acid substitution at codon 132 of the IDH1 protein: IDH1 p.R132X.

Clinical claim:

Testing DNA from tumour tissue to detect IDH1 p.R132X tier 1 variant, followed by targeted therapy with ivosidenib results in superior health outcomes compared to no testing and untargeted treatment/best supportive care in patients with locally advanced or metastatic CCAs.

PICO criteria

Population

Cholangiocarcinomas (CCAs), also known as bile duct cancers, are rare cancers that arise from the epithelial cells of the bile ducts. Bile ducts are a group of small tubes through which the bile (a digestive fluid produced in the liver) flows to the gallbladder and eventually into the small intestine. CCAs are divided into two subtypes: the intrahepatic CCAs (iCCAs) and the extrahepatic CCAs (eCCAs), according to the original location of

the cancer. iCCAs are tumour lesions that develop within the liver and are the second most common primary liver tumour after hepatoma. eCCAs are lesions that originate from bile ducts outside of the liver. eCCAs include perihilar lesions (pCCAs) that are located around the hilar region of the biliary tree and the common bile duct, and distal lesions (dCCAs) that occur at the more distal part of the common bile duct (Forner et al. 2019).

CCAs are scarce and comprise approximately 3% of all gastrointestinal cancers (Banales et al. 2020). They have a global incidence of 0.3-6 per 100,000 people per year, although in countries such as China, South Korea and Thailand, the incidence can be greater than 6 per 100,000 people per year. (Banales et al. 2020). The cancer typically affects individuals aged between 50 and 70 years, and males are slightly more affected than females (Van Dyke et al. 2019). pCCA has been reported to be the most common type of CCA in the USA (50-60% of all CCAs), followed by dCCA (20-30%) and iCCA (10-20%) (Banales et al. 2016). In Australia, the true incidence of iCCA and eCCAs is unknown. The applicant estimated that around 1,161 new cases of CCAs were diagnosed in Australia in 2022 based on data from the Australian Institute of Health and Welfare (AIHW)¹. However, given that CCAs are typically diagnosed when already at an advanced stage (see below) it can be difficult to distinguish 'new' cases from pre-existing cases which have already progressed to an advanced stage.

Despite being uncommon, the incidence of CCAs has been rising in the past few decades worldwide, likely owing to an increased population with the conditions that cause chronic liver inflammation. This trend is more obvious for iCCA (Forner et al. 2019). While in many patients no specific risk factor can be identified (Chapman 1999), cirrhosis, hepatitis B and C, excess alcohol, obesity and diabetes have been found to have association with development of iCCA (Forner et al. 2019).

Primary sclerosing cholangitis (PSC), despite its rarity, is recognised as a main risk factor for development of CCAs. PSC was found to account for a 240-fold increased risk for development of the cancer and its related death in an Australian retrospective cohort study (Tan et al. 2022). PSC has a prevalence of approximately 2.8% in patients with ulcerative colitis (UC), a form of inflammatory bowel disease (Barberio et al. 2021). The prevalence of UC reported in an Australian cross-sectional study was 334 per 100,000 and has been increasing in recent decades, with males having greater risk (Busingye, Pollack & Chidwick 2021). People with rare congenital abnormalities of the biliary tree such as choledochal cyst and Caroli disease (incidence is higher among Asians) also carry higher risk for development of CCAs (Forner et al. 2019).

CCAs are among those cancers that have a dismal prognosis partly because patients are frequently asymptomatic until the disease is in its advanced stages (Banales et al. 2016). Only approximately 35% of patients are detected with early stage disease (Li, Song & Liu 2022). Among these patients who have a resectable tumour at presentation and undergo surgical resection (the only potentially curative option), the relapse rate is high, ranging between 42% to 70% (Lamarca et al. 2020b; Primrose et al. 2019) with a 5-year survival rate for localised CCA of only 23% in 2018². The cancer was also found to frequently recur at a distant site (Horgan et al. 2012; Koerkamp et al. 2015). The American Cancer Society³ reported that the overall 5-year relative survival rate was only 11% for those diagnosed with eCCA between 2012 to 2018. The 5-year survival rates for localised disease, eCCA that has spread to the regional lymph nodes (locally advanced) and

¹ Australian Institute of Health and Welfare URL: <https://www.aihw.gov.au/>

² The Australian Cancer Research Foundation: Bile Duct Cancer URL: <https://www.acrf.com.au/support-cancer-research/types-of-cancer/bile-duct-cancer/> [Accessed 13 June 2023]

³ American Cancer Society: Survival Rates for Bile Duct Cancer URL: <https://www.cancer.org/cancer/types/bile-duct-cancer/detection-diagnosis-staging/survival-by-stage.html>. [Accessed 13 June 2023]

metastatic eCCA were 18%, 18% and 2%, respectively. The Australian Cancer Research Foundation² reported the 5-year survival rate for eCCA in Australia was 15% in 2018. The American Cancer Society also reported that patients diagnosed with iCCA, the 5-year survival rates for overall, localised, locally advanced and metastatic disease were 9%, 23%, 9% and 2% respectively. No Australian survival data specific for iCCA were identified.

Signs and symptoms of CCA depend upon the location of the tumour lesion. Patients with eCCA commonly present with jaundice (yellowish or greenish pigmentation of the skin and the mucous membranes) due to the obstruction of the bile outflow. Other signs and symptoms indicating bile outflow obstruction include pale stools, dark urine and pruritus (Forner et al. 2019). Patients with iCCA can also present with jaundice but usually at a later stage, while a significant proportion of iCCA cases are incidental findings, especially in early stages (Cardinale et al. 2018). Other than jaundice, symptoms associated with CCA can include abdominal pain, fatigue, night sweats, nausea, and weight loss. Liver function testing may show abnormalities in early stages of the disease (Forner et al. 2019).

The poor prognosis associated with CCAs, especially for patients diagnosed with advanced stage disease, is likely due to the limited treatment options available. For these groups of patients, very limited systemic therapy options are available as second or third-line treatments. There are currently no targeted therapy options available in Australia.

Management of CCA patients in the lead up to IDH1 p.R132X tier 1 variant testing of tumour tissue

Symptomatic patients are assessed by general practitioners (GPs) to evaluate the presence of jaundice and to look for signs of chronic liver dysfunction through physical examination (Fargo, Grogan & Saguil 2017). When necessary, laboratory investigation (including liver function tests and serum bilirubin level) and imaging studies (likely to be ultrasound or computed tomography (CT)), will be organised to further evaluate the presence of cholestasis (caused by bile outflow obstruction) and its possible aetiology. Patients with specific findings will be referred to specialists' services, where further imaging studies will be arranged to confirm the presence of a tumour causing the biliary obstruction and for staging purposes in case of a malignancy. These studies can include magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), cholangiography (endoscopic or percutaneous), or positron emission tomography (PET). The cancer is staged according to the TNM classification system developed by the American Joint Committee on Cancer (AJCC), where T reflects the extent of the primary tumour, N is the extent of regional lymph node infiltration and M indicates the presence of distant metastases (American Cancer Society 2022).

Once the presence of a tumour is confirmed, the investigation typically proceeds to a biopsy of the tumour to further investigate its cellular nature by a pathologist for a tissue diagnosis to be established. Biopsy can be done through a variety of means such as brush cytology, fine needle aspiration or CT/MRI-guided biopsy (Forner et al. 2019). The National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) have recommended testing for IDH1 p.R132X variant status of tumour tissue as part of the routine diagnostic procedure for patients with CCAs, particularly for those with confirmed locally advanced or metastatic CCAs and will receive systemic therapy as their first-line treatment (NCCN 2023; Vogel et al. 2023). Where feasible and safe, core biopsy is recommended, in order to obtain sufficient tissue for IDH1 testing (Lamarca, Edeline & Goyal 2022; Vogel et al. 2023).

PASC suggested that all patients with newly diagnosed and histologically confirmed CCA, should have their tumour tissue tested for IDH1 tier 1 variant status regardless of cancer stage or subtype, given the high relapse rate of early stage CCA and the relatively small number of patients diagnosed with the cancer. For patients who have been previously diagnosed with CCA of earlier stages, the applicants propose that tissue

blocks will be retrieved and tested upon progression to locally advanced or metastatic CCA. In the key trial of ivosidenib, participants' *IDH1* testing was carried out by next-generation sequencing (NGS) on formalin-fixed, paraffin-embedded (FFPE) tumour tissue. The tissue samples were either archival or from fresh tumour biopsy (Zhu et al. 2021). Carrick et al (2015) have demonstrated the feasibility and reliability of conducting NGS on older FFPE tumour tissue samples in their study, regardless of storage time.

Biological rationale for targeting IDH1 p.R132X tier 1 variants with ivosidenib

The IDH family of metabolic enzymes comprises three isozymes (IDH1, IDH2 and IDH3) that convert isocitrate to α -ketoglutarate (α -KG) via oxidative decarboxylation and are essential for cellular respiration in the tricarboxylic acid cycle. IDH1 is located in the cytosol and IDH2 and IDH3 are located in the mitochondria. *IDH1* variants usually occur due to a nucleotide substitution at position 394 and/or 395 of the deoxyribonucleic acid (DNA) sequence, leading to a single amino acid substitution of arginine (R) at position 132 of the IDH1 protein (*IDH1*^{R132X}). These 'gain-of-function' *IDH1* p.R132X variants lead to the disruption of the normal catalytic activity, and an increased conversion of α -ketoglutarate (α -KG) to 2-hydroxyglutarate (2-HG), as shown in Figure 1.

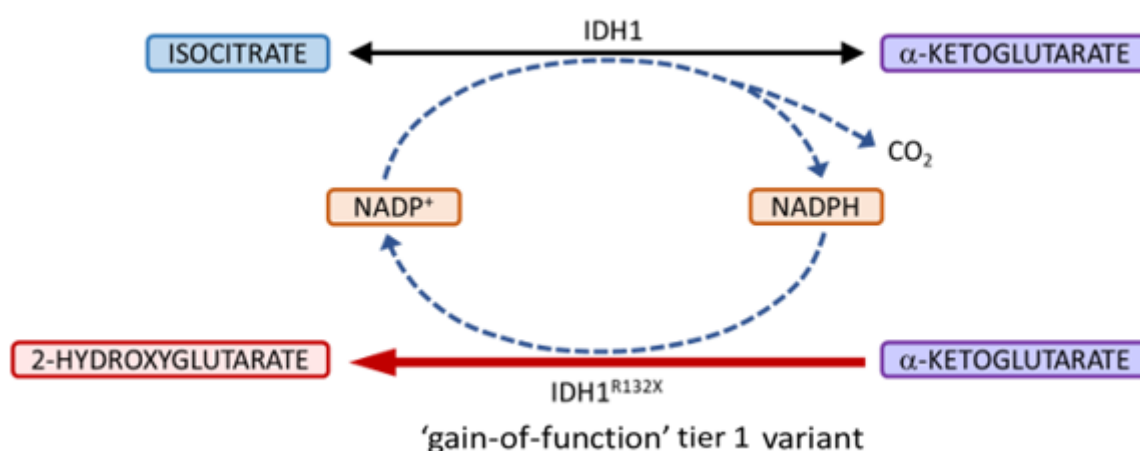


Figure 1 Schematic representation of the impact of *IDH1* p.R132X tier 1 variants on the accumulation of 2-hydroxyglutarate (2-HG)

Source: adapted form (Rizzo, Ricci & Brandi 2021)

2-HG acts as an oncometabolite, promoting tumour proliferation and metastasis development through several pathways, such as DNA methylation and activation of vascular endothelial growth factor receptor (VEGFR) (Salati et al. 2020). Additionally, lower levels of α -KG can inhibit the degradation of hypoxia-inducible factor 1 α (HIF-1 α) leading to aberrant cellular proliferation and enhancement of angiogenesis and tumourigenesis.

A *IDH1* p.R132X variant is now recognized as a “driver mutation” required for the initiation of tumourigenesis in low-grade gliomas (Molloy et al. 2020). Dang, Yen & Attar (2016) reported that the amino acid substitutions leading to gain-of-function *IDH1* p.R132X variants were broad, including (but not limited to) polar amino acids (H, C, K, S, T, Q) and bulky nonpolar amino acids (W, V, M), and speculated that the structural location was more important than the intrinsic nature of the substituted codons.

Johnson et al. (2014) compared the genetic profile of primary and recurrent tumours from 23 patients with low grade primary gliomas and found that initial and recurrent gliomas displayed a broad spectrum of genetic relatedness but *IDH1* p.R132X variants were the only shared genetic variant present in both the primary tumour and matched tumour recurrences in every patient. This result indicates that *IDH1* p.R132X

variants are likely to be “driver mutations” in gliomagenesis and suggests that this genetic biomarker is very stable throughout disease progression for glioma. No studies looking at its stability in CCA were identified. However, the IDH1 p.R132X biomarker was found to also be a driver mutation in CCA by Makawita et al. (2021). Thus, although its stability in CCA is unknown, the similarity in the mode of action of the IDH1 p.R132H biomarker in glioma and CCA suggests that it may also be stable throughout disease progression in CCA.

IDH1 p.R132C is the most common tier 1 variant found in CCA, comprising 69% of all IDH1 p.R132X variants. Other less frequent IDH1 p.R132X variants include p.R132L (16%), p.R132G (7%), p.R132S (4%), p.R132H (3%) and p.R132F (< 1%) (Makawita et al. 2021).

Although the frequency varies between studies, up to 20% of iCCA and 3% of eCCA are expected to harbour an IDH1 p.R132X tier 1 variant and would be eligible for targeted therapy with ivosidenib following progression after first-line systemic therapy (Lamarca, Barriuso, et al. 2020; Zhu et al. 2021).

Intervention

Test

The proposed medical service, *IDH1* testing, involves testing for the presence of a genetic variant resulting in a IDH1 p.R132X variant in FFPE CCA tissue samples, either from fresh tumour biopsy, cytology washings or archival tissue blocks. If inadequate tumour sample is available, a re-biopsy would be required to provide a tissue sample for testing. The test results will serve to determine the patients’ eligibility for PBS-subsidised ivosidenib (Tibsovo®) treatment either when diagnosed with, or on progression to, locally advanced or metastatic CCA. *IDH1* testing is proposed to be delivered only once in a patient’s lifetime.

PASC advised the IDH1 testing is aimed to be delivered to all histologically confirmed CCA tissue at primary diagnosis of the cancer, regardless of stage or subtype, in order to:

- *streamline the diagnostic process,*
- *allow more effective use of diagnostic tissue, and*
- *reduce the need for block retrieval.*

PASC considered this approach will potentially reduce or allow earlier planning for re-biopsy and a quicker transition to ivosidenib for patients who have disease progression following untargeted anti-cancer treatment. Performing the testing at the outset also has the potential to reduce the negative psychological impact of a negative test result on a patient who has just received a diagnosis of disease progression. The option of performing IDH1 testing on archival tissue blocks will address the issue of equity of access for patients who have cancer recurrence but whose tumour tissues were not tested previously for IDH1 p.R132X variant status and are not suitable to undergo re-biopsy at the time of disease progress for various reasons.

Currently, *IDH1* testing of FFPE tumour tissues utilising DNA sequencing methods is only available on the MBS for patients with gliomas whose tumours do not have the IDH1 p.R132H variant on prior testing with immunohistochemistry (IHC). IDH1 p.R132H is the most prevalent pathogenic variant in gliomas and can be accurately detected by IHC (Capper et al. 2010; Idbaih & Touat 2016). Currently, three diagnostic laboratories listed on the Royal College of Pathologists of Australasia (RCPA) website conduct *IDH1* testing. Two use Sanger sequencing to detect IDH1 p.R132X-associated genetic variants associated with AML. The third laboratory uses pyrosequencing to detect IDH1 p.R132X-associated genetic variants in glioma FFPE samples. Purified DNA from the tissue sample is amplified using polymerase chain reaction (PCR) before being sequenced by Sanger sequencing or pyrosequencing. The turnaround time of this testing is 1-2 weeks (RCPA

2023). Pyrosequencing is an early NGS DNA sequencing method based on the emission of light when luciferin is converted to oxyluciferin with the intensity reflecting the number and type of nucleotides added (Ronaghi, Uhlén & Nyrén 1998). Pyrosequencing has been shown to be a DNA sequencing method with high applicability, reproducibility, and accuracy in detecting single nucleotide polymorphisms in *IDH1* at R132 in clinical samples (Fakhrai-Rad, Pourmand & Ronaghi 2002; Setty et al. 2010).

Another sequencing method that is used in Australian pathology laboratories is NGS, a high-throughput DNA (and/or ribonucleic acid (RNA)) sequencing method that allows sequencing of many target genes at the same time. NGS typically involves 4 steps: (1) Constructing the DNA “library”; (2) amplifying the library clonally; (3) sequencing the library, and (4) analysing data. Compared with Sanger sequencing, NGS methods are more cost-effective⁴. There can also be flexibility for *IDH1* testing to be performed as part of a gene panel using NGS. *Given the higher sensitivity of NGS and pyrosequencing, these two methods will most likely be used to carry out IDH1 testing on CCA tumour tissues. PASC discussed that the IDH1 testing would commonly be performed as part of an NGS panel, incorporating other variants which may have prognostic implications. The testing may be either DNA- or RNA based. RNA degrades quickly, so testing the tissue sample at the point of diagnosis rather than at the point of progression would be better.*

IHC testing is used to detect *IDH1* p.R132H aberrant protein in glioma. This test is not useful in detecting any other *IDH1* p.R132X variants. As the *IDH1* p.R132H variant only accounts for 3% of all *IDH1* p.R132X variants, IHC is not a useful test in CCA (Makawita et al. 2021).

*PASC discussed the appropriate genetic terminology to describe the variants in question, which were somatic tier 1 variants only in this case. PASC noted the MSAC guidelines (2021) state that somatic variants should be described in terms of their clinical significance (Tier I variants having strong clinical significance). PASC noted the clinical advice provided by the Applicants, that clinicians were more likely to understand “pathogenic” (in both somatic and germline settings), rather than Tiers. PASC noted that the clinical significance of the variant captures a different concept than the pathogenicity of the variant, as it includes whether there is a treatment available in response to knowledge of the variant. In this sense, the *IDH1* p.R132X variants of interest, and have Tier 1 clinical significance. PASC questioned whether both “pathogenic” and “tier 1” should be used in the item descriptor but considered when determining tier status to assign to a variant, the variant is first classified as to pathogenicity/oncogenicity based on variant-level evidence, and then the tier is assigned in the second step based on tumour and treatment parameters and previous variant classification. PASC suggested that tier 1 should be the correct term to use. PASC advised that variant classification should follow a recommended guideline. Wording of the proposed testing was finalised as “*IDH1* p.R132X tier 1 variant testing” in the PICO confirmation. PASC noted the current MBS item descriptor states “pathological” variants, which is incorrect terminology. PASC considered that the wording should convey that genetic methods were in scope for the proposed testing.*

PASC suggested that the testing should be pathologist determinable, to streamline the characterisation of the tumour. PASC considered this pragmatic approach would avoid the need for block retrieval at a later

⁴ What is Next-Generation Sequencing (NGS)? URL: [https://www.thermofisher.com/au/en/home/life-science/sequencing/sequencing-learning-center/next-generation-sequencing-information/ngs-basics/what-is-next-generation-sequencing.html#:~:text=Next%2Dgeneration%20sequencing%20\(NGS\),diseases%20or%20other%20biological%20phenomena](https://www.thermofisher.com/au/en/home/life-science/sequencing/sequencing-learning-center/next-generation-sequencing-information/ngs-basics/what-is-next-generation-sequencing.html#:~:text=Next%2Dgeneration%20sequencing%20(NGS),diseases%20or%20other%20biological%20phenomena). [Accessed 3 July 2023]

timepoint. PASC noted that the applicants also agreed it was appropriate that pathologists ordered the test to streamline the process.

Treatment

For patients initially diagnosed with inoperable CCAs (i.e., the locally advanced or metastatic CCAs) and patients with recurrent CCAs after surgical resection whose cancer has progressed to an advanced stage, systemic chemotherapy is the primary therapeutic strategy. The standard of care first-line chemotherapy regimen for these patients is cisplatin plus gemcitabine (the 'CisGem' regimen) provided that the patient has adequate hepatic and renal function and a performance status (Eastern Cooperative Oncology Group [ECOG]) score <2 (eviQ 2022b; Valle et al. 2010). For patients with significant co-morbidities, inadequate hepatic or renal function or performance status (ECOG score ≥ 2), or patients with other contraindication for cisplatin, gemcitabine monotherapy or carboplatin plus gemcitabine are preferred over CisGem (eviQ 2022a; Lamarca, Edeline & Goyal 2022). Treatment with CisGem for patients with advanced or metastatic CCAs was found to be associated with a median progression-free survival of 8 months (Valle et al. 2010).

Ivosidenib (Tibsovo®) is currently registered under Therapeutic Goods Administration (TGA) as a medicine for anti-cancer targeted therapy and is approved for the treatment of adult patients with locally advanced or metastatic CCA with an IDH1 p.R132X variant, after at least one prior line of systemic therapy².

Ivosidenib is an oral inhibitor of the 'gain-of-function' IDH1 p.R132X and its action results in a decrease of cellular 2-HG levels in a dose-dependent manner (Popovici-Muller et al. 2018). The oncometabolite 2-HG is responsible for changes in gene regulation and impaired cellular differentiation.

Clinical utility standard

The test method used in the ClarIDHy trial to identify patients with an IDH1 p.R132X genetic variant was NGS using the Oncomine Focus Assay (Thermo Fisher Scientific) with either archival or fresh FFPE tumour samples (Zhu et al. 2021).

Comparators

Test

For patients with CCA, there is no molecular testing in the current clinical management pathway. Therefore, the comparator for the proposed *IDH1* testing is 'no testing'.

PASC agreed on "no testing" as the comparator to the proposed IDH1 testing.

Treatment

The applicant has indicated that targeted therapy with ivosidenib would occur after disease progression following either first- or second line chemotherapy and suggested that it is most likely to occur after first-line therapy in the majority of patients. The comparator to therapy with ivosidenib proposed by the applicant is palliative care. The applicant's rationale for this is provided in Appendix 1.

Chemotherapy with 5-FU and oxaliplatin (FOLFOX) or 5-FU plus irinotecan (FOLFIRI) is the current recommended second-line regimen.^{5,6} The applicant reported that less than 45% of patients who failed first-line therapy would receive the second-line chemotherapy (see Appendix 1). Thus, chemotherapy with FOLFOX or FOLFIRI is a secondary comparator for patients receiving ivosidenib in the second line.

PASC agreed on (1) palliative care as the primary comparator to ivosidenib in the second-line or third-line treatment setting when patient's disease progresses after chemotherapy, and (2) chemotherapy with 5-FU and oxaliplatin (FOLFOX) or 5-FU plus irinotecan (FOLFIRI) as the secondary comparator to ivosidenib in the second-line treatment setting when patient's disease progresses on the first-line chemotherapy.

Outcomes

Test-related outcomes

At the May 2023 MSAC Executive meeting, the department sought advice as to whether the assessment of Application 1750 should include consideration of the stability of the biomarker or comparative analytical performance of the different molecular methods for *IDH1* testing. The MSAC Executive considered that it was not necessary to assess comparative analytical performance across the different molecular methods for this application.

Clinical utility of the test

- Treatment effect modification for ivosidenib based on *IDH1* p.R132X variant status (predictive validity)

Other test-related considerations:

- Number estimated to be tested
- Number needed to test (to identify one case eligible for treatment)
- Test turn-around time
- Rate of re-biopsy (including test failure and inadequate sample rate)
- Safety of re-biopsy

Treatment-related outcomes

Critical outcomes (GRADE)

- Progression-free survival (PFS)
- Overall survival (OS) (unadjusted OS and RPSFT-adjusted OS)
- Objective response rate (ORR)

Important outcomes (GRADE)

- Time from randomisation to study treatment discontinuation or death (TDT)

⁵ <https://www.eviq.org.au/medical-oncology/upper-gastrointestinal/pancreas-and-biliary/3875-biliary-and-gallbladder-advanced-folfox6-mod> [Accessed 30 Jun 2023]

⁶ Cancer Institute of NSW, EviQ Pancreas and biliary medical oncology. URL: <https://www.eviq.org.au/medical-oncology/upper-gastrointestinal/gastric-and-oesophageal-metastatic/4043-advanced-or-metastatic-folfiri-modified-fl#indications-and-patient-population-biliary-and-g> [Accessed 30 Jun 2023]

- Health-related quality of life (HRQoL)

Safety and tolerability

- Treatment-emergent adverse events (TEAEs)
- Physical examination and laboratory findings
-

Healthcare system

- Cost of testing and associated re-biopsies per patient
- Cost-effectiveness of testing and treatment
- Financial implications

PASC agreed on the proposed outcomes. PASC noted that the outcomes were related to the predictive validity of the test, and that aspects of test accuracy were not required to be assessed.

Assessment framework

The aim of the codependent submission will be to demonstrate that testing for IDH1 p.R132X variants and targeted treatment with ivosidenib results in superior health outcomes compared to no testing and palliative care/untargeted treatment in patients with locally advanced or metastatic CCA. The key trial, ClarIDHy, is a randomised trial comparing ivosidenib versus placebo in patients with IDH1 p.R132X variants. This provides incomplete direct evidence (i.e. health outcomes only for those who test positive for IDH1 p.R132X variants), and does not make the relationship between the biomarker and medicine explicit. Further evidence will be required to supplement the key trial, in order to demonstrate that the medicine interacts with the biomarker (either directly through clinical evidence, or from *in vitro* studies, or by inference (e.g., if there is a biologically plausible basis to differentiate between those with and without IDH1 p.R132X variants and response to the medicine)), as per Product type 4 of the PBAC guidelines.

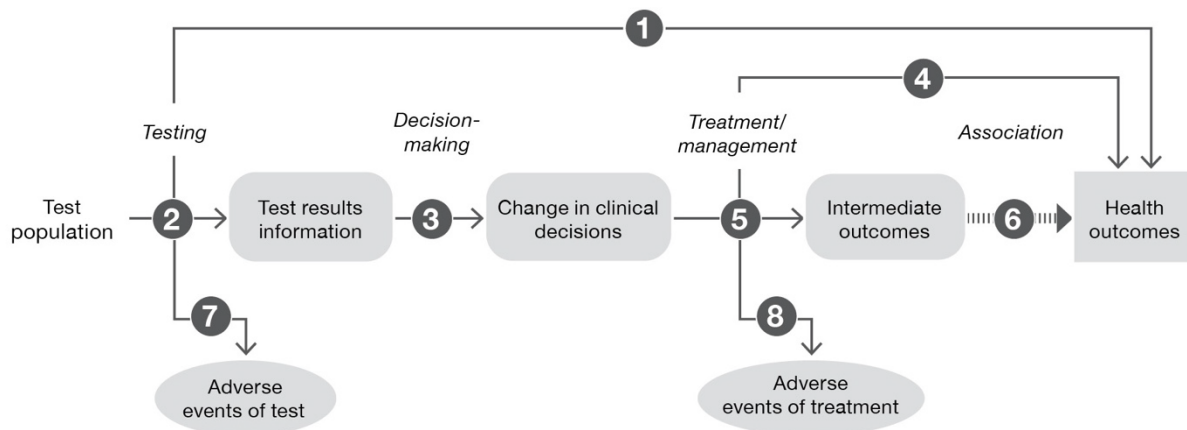


Figure 2 Generic assessment framework showing the links from the test population to health outcomes

Figure notes: 1: direct from test to health outcomes evidence; 2: test accuracy; 3: change in diagnosis/treatment/management; 4: influence of the change in management on health outcomes; 5: influence of the change in management on intermediate outcomes; 6: association of intermediate outcomes with health outcomes; 7: adverse events due to testing; 8: adverse events due to treatment

Research questions mapped to the assessment framework:

1. What is the safety and effectiveness of *IDH1* testing and targeted treatment with ivosidenib versus no testing and palliative care or second-line chemotherapy in patients with locally advanced or metastatic CCA who have failed first- or second-line chemotherapy? (Direct evidence)
2. What is the diagnostic yield of *IDH1* testing in patients with locally advanced or metastatic CCA? (or the number needed to test to find one patient eligible for ivosidenib)
Do results from *IDH1* testing predict a treatment effect modification with ivosidenib?
3. What proportion of patients eligible for ivosidenib based on variant status, meet all other eligibility criteria, and receive the treatment? (*note, evidence that patients are treated consistent with test results may be assumed for a codependent biomarker and medicine*).
4. What is the effectiveness of ivosidenib vs palliative care or second-line chemotherapy for overall survival in those locally advanced or metastatic CCA who have failed first- or second-line chemotherapy and have *IDH1* pR.132X variants?
5. What is the effectiveness of ivosidenib versus palliative care or second-line chemotherapy on the outcomes of progression-free survival and objective response rate in those locally advanced or metastatic CCA who have failed first- or second-line chemotherapy and have *IDH1* pR.132X variants? (*if required*)
6. How valid is the link between progression-free survival or objective response rate and overall survival in patients with CCA? (*if claim is based on these outcomes rather than overall survival*)
7. Rate of re-biopsy required due to insufficient tissue available for testing, and any adverse events associated with re-biopsy?
8. What is the safety of ivosidenib vs palliative care or second-line chemotherapy for overall survival in those locally advanced or metastatic CCA who have failed first- or second-line chemotherapy and have *IDH1* pR.132X variants?

PASC agreed on the proposed assessment framework.

Clinical management algorithms

Current clinical management algorithm for the identified population

In the absence of Australian specific guidelines for the treatment of advanced or metastatic CCA, the clinical management algorithm (Figure 3) was developed according to current EviQ treatment protocols⁷, which take into account the Australian specific PBS restrictions and Product Information criteria, and the 2023 National Compressive Cancer Network (NCCN) guidelines⁸.

Two first-line chemotherapy regimen options for advanced or metastatic CCA are endorsed by EviQ and/or NCCN: Gemcitabine and cisplatin, or gemcitabine monotherapy.

For patients with adequate performance status and liver function (which is reflected by patient's serum bilirubin level being less than 1.5 times of upper normal limit), gemcitabine and cisplatin ('CisGem') is the preferred first-line chemotherapy regimen over gemcitabine monotherapy, due to the survival benefit

⁷ Cancer Institute of NSW, EviQ Pancreas and biliary medical oncology. Available from URL: <https://www.eviq.org.au/medical-oncology/upper-gastrointestinal/pancreas-and-biliary> [Accessed 20 June 2023]

⁸ National Comprehensive Cancer Network. Available from URL: https://www.nccn.org/login?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/btc.pdf [Accessed 20 June 2023]

shown in a clinical trial (Valle et al. 2010). In patients with performance status 2 or above, impaired liver function, significant comorbidities, or contraindication to cisplatin (including pre-existing renal impairment, hearing impairment, myelosuppression or allergic reactions to cisplatin or other platinum-containing compounds), gemcitabine monotherapy is the preferred option of treatment (Lamarca, Edeline & Goyal 2022). EviQ also endorsed the combination of carboplatin and gemcitabine as an option for patients with contraindication to cisplatin, based on the results of a phase II single institution study (Williams et al. 2010).

For patients whose cancer does not respond to, or relapses after, first-line treatment, the clinical management options include chemotherapy with FOLFOX6 (modified) (fluorouracil, leucovorin and oxaliplatin) and palliative care. Patients treated with FOLFOX6 in addition to active symptom control showed improved overall survival compared with active symptom control alone in a clinical trial, after progression on CisGem treatment (Lamarca et al. 2021). FOLFOX6 regimen is preferred for patients with good performance status who choose to continue with anti-cancer treatment. For patients whose performance status is inadequate, palliative care with best symptom control is the option to preserve quality of life. For patients with progressive cancer after CisGem treatment and whose performance status and hepatic function are adequate, EviQ have approved the FORFIRI (modified) (fluorouracil, leucovorin and irinotecan) regimen as an alternative for anti-cancer treatment, based on the results of a randomised phase II study (Choi et al. 2021).

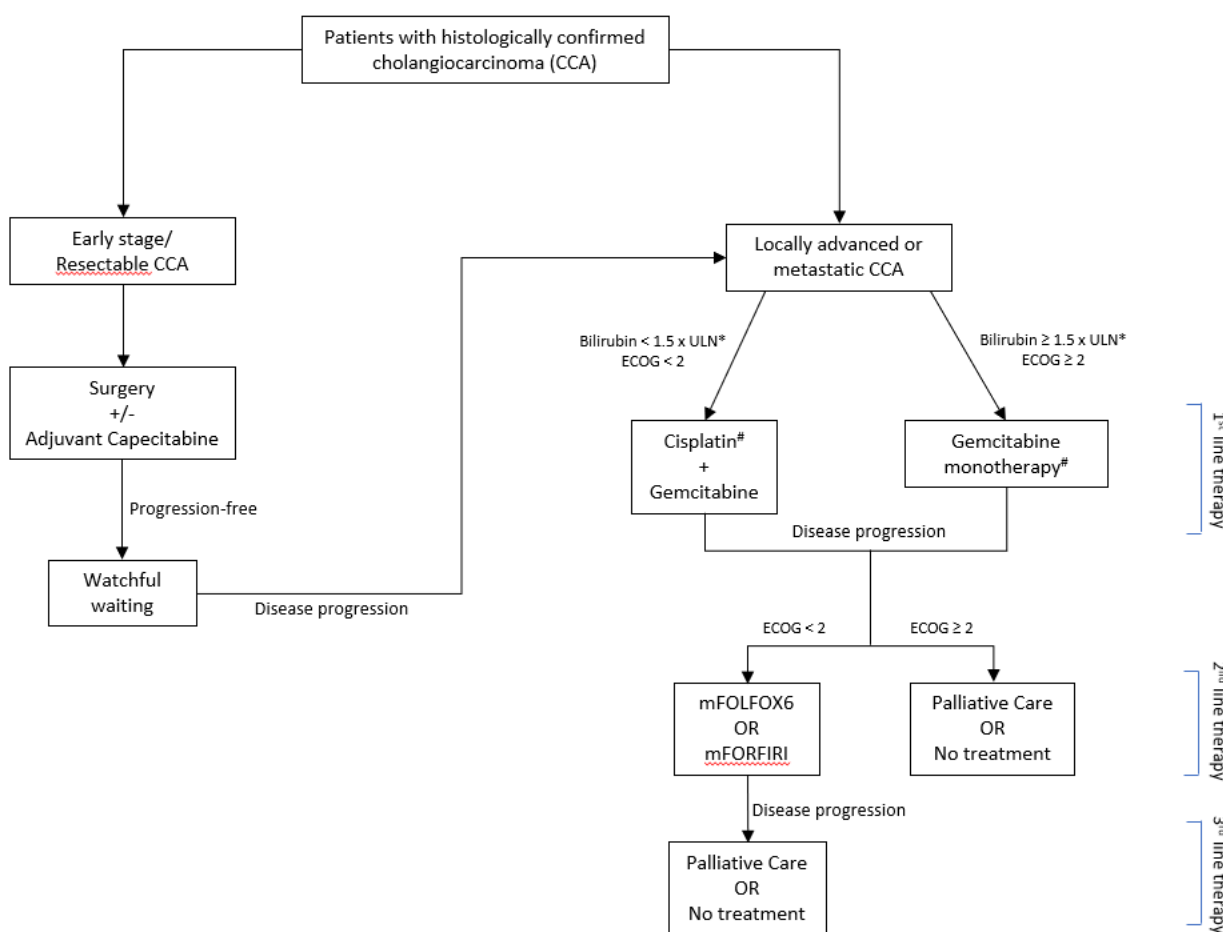


Figure 3 Current clinical management algorithm of advanced stage or metastatic cholangiocarcinoma

Lamarca, A, Edeline, J & Goyal, L 2022, 'How I treat biliary tract cancer', *ESMO Open*, vol. 7, no. 1, Feb, p. 100378.

* In patients with contraindication to cisplatin (including preexisting renal impairment, hearing impairment, myelosuppression or allergic reactions to cisplatin or other platinum-containing compounds), options include substituting carboplatin for cisplatin or gemcitabine monotherapy.

Proposed clinical management algorithm for the identified population

The NCCN guideline recommends that all patients diagnosed with locally advanced or metastatic CCA receive molecular testing as part of their diagnostic process (NCCN 2023). In the proposed algorithm (Figure 4), *IDH1* testing is implemented for all patients at diagnosis of CCA.

Patients in whom an *IDH1* p.R132X variant was identified would be eligible for targeted therapy with ivosidenib after disease progression following first-line or second-line chemotherapy. For patients without an *IDH1* p.R132X variant, treatment options after disease progression following first-line or second-line chemotherapy remain unchanged.

PASC confirmed that the proposed *IDH1* testing will be aimed to be delivered to all histologically confirmed CCA tissue at primary diagnosis of the cancer, regardless of stage or subtype, in order to streamline the diagnostic process, allow more effective use of diagnostic tissue, and reduce the need for block retrieval. This approach will potentially reduce or allow earlier planning for re-biopsy and a quicker transition to ivosidenib for patients who have disease progression following untargeted anti-cancer treatment. Performing the testing at the outset also has the potential to reduce the negative psychological impact of a negative test result on a patient who has just received a diagnosis of disease progression. The option of performing *IDH1* testing on archival tissue blocks will address the issue of equity of access for patients who have cancer recurrence but whose tumour tissues were not tested for their *IDH1* p.R132X variant status and are not suitable to undergo re-biopsy at the time of disease progression for various reasons.

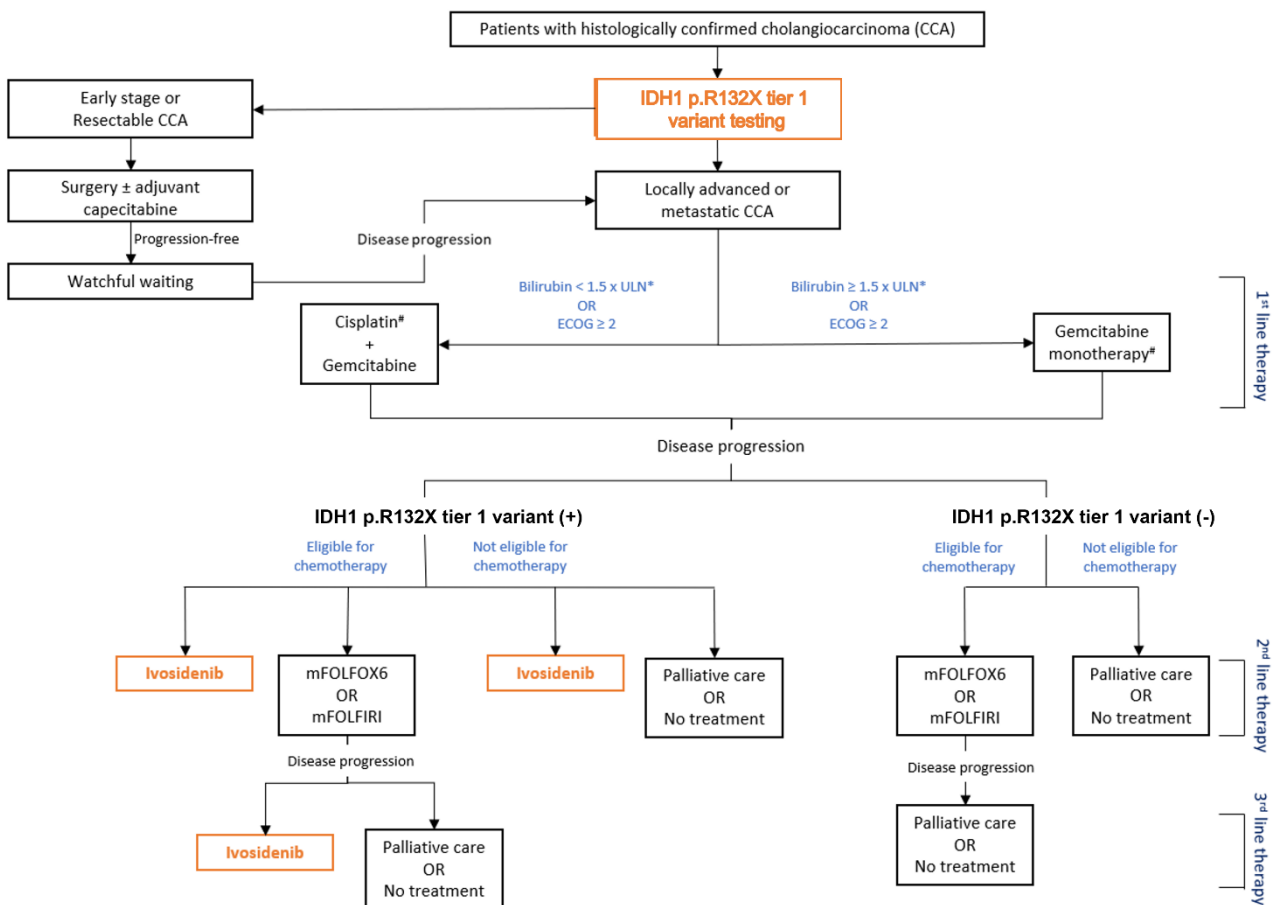


Figure 4 Proposed clinical management algorithm of advanced stage or metastatic CCA

* Lamarca, A, Edeline, J & Goyal, L 2022, 'How I treat biliary tract cancer', ESMO Open, vol. 7, no. 1, Feb, p. 100378.

In patients with contraindication to cisplatin (including pre-existing renal impairment, hearing impairment, myelosuppression or allergic reactions to cisplatin or other platinum-containing compounds), options include substituting carboplatin for cisplatin or gemcitabine monotherapy.

Proposed economic evaluation

The overall clinical claim is that the proposed codependent technologies (*IDH1* testing and ivosidenib as targeted therapy) are **superior** in terms of overall survival, compared with no testing and untargeted treatment (this includes second-line chemotherapy with FOLFOX6 or FORFIRI, and palliative care with active symptom control) in patients with advanced or metastatic CCA whose disease does not respond to first or second-line chemotherapy and whose tumours have tested positive for an *IDH1* p.R132X variant. Given the claim of clinical superiority, the appropriate type of economic evaluation to be included in the assessment report would be either a cost-effectiveness analysis (CEA) or a cost-utility analysis (CUA). The impact of delivering the test at time of primary diagnosis to all histologically confirmed CCA tissues on CEA/CUA will be negligible.

PASC noted that the impact of testing timing on the CEA/CUA will likely be negligible.

Proposal for public funding

Currently, the proposed *IDH1* variant test is available under MBS item number 73372 for patients with gliomas (Table 2).

Table 2 Current MBS item descriptor for *IDH1* variant testing

Category 6 – Pathology Services	
MBS item number 73372	Group P7 - Genetics
Analysis of tumour tissue, requested by a specialist or consultant physician, that is for: Identification of <i>IDH1/2</i> “pathological” variant status; and A patient with: (1) negative <i>IDH1</i> (R132H) immunohistochemistry; and (2) clinical or laboratory evidence, including morphological features, of glial neoplasm Applicable only once per lifetime	
Fee: \$340.00 Benefit: 75% = \$255.00 85% = \$289.00	

The proposed MBS item descriptor for *IDH1* variant testing in patients with cholangiocarcinoma is shown in Table 3.

Table 3: Proposed MBS item descriptor

Category 6 – Pathology Services	
Proposed item descriptor	Group P7 - Genetics
Detection in tumour tissue of <i>IDH1</i> p.R132X tier 1 variant status, in a patient with histologically confirmed cholangiocarcinoma, to determine access to an isocitrate dehydrogenase I inhibitor under the Pharmaceutical Benefits Scheme (PBS). Applicable only once per lifetime	
Fee: \$340.00 Benefit: 75% = \$255.00 85% = \$289.00	

PASC agreed on the item descriptor being silent on test methodology. PASC noted that “ivosidenib” was specifically proposed for the treatment but considered that broadening this would futureproof the MBS item descriptor, and that other IDH1 inhibitors would also likely have effect based on the presence of a p.R132X variant, and so advised this should be generalised to “isocitrate dehydrogenase I inhibitor”.

IDH1 testing is likely to be conducted in specialist laboratories who must hold the appropriate accreditation and registration for this testing procedure to receive MBS funding for the proposed test. Laboratories will need to participate in the relevant Royal College of Pathologist of Australasia (RCPA) Quality Assurance Program or a similar external quality assurance program. Testing must be conducted, and the results interpreted and reported by suitably qualified and trained molecular pathologists.

PASC noted that although the item descriptor mentions testing of tumour tissue, this is understood to also include cytology samples.

It is expected that a patient will only be tested for IDH1 p.R132X variant status once in their lifetime. PASC confirmed that, based on glioma biomarker stability data, the frequency restrictor of not more than once per lifetime for IDH1 testing, is appropriate.

As discussed previously PASC considered that the item should be made pathologist determinable.

PASC has given advice that the proposed fee in the codependent submission is adequate for testing CCA tissue samples. NGS or pyrosequencing will most likely be the methods used for the testing.

Summary of public consultation input

PASC noted and welcomed consultation input from 1 organisation and 2 individuals who identified as health professionals (pathologists). The 1 organisation that submitted input was:

- *Pancare Foundation*

All the consultation feedback received was strongly supportive of public funding for testing of tumour tissue to detect *IDH1* mutations in patients with cholangiocarcinoma to determine eligibility for ivosidenib on the PBS.

Clinical need and public health significance

The main benefits of public funding received in the consultation feedback included improved quality of life, improved progression-free survival and overall survival and an opportunity for patients to spend time with family. The feedback noted that the targeted therapy has been shown to be well tolerated and effective in robust international clinical trials and that it provides hope for patients and their families. Pancare stated that public funding would lessen the financial toxicity associated rare cancers and offer patients equitable access to additional pathways to alter disease progression.

Pancare did not see any disadvantage to the proposed medical service, with one individual noting that patients found to be negative for an *IDH1* pathogenic variant may be devastated at not being able to receive targeted therapy.

Pancare identified genetic counselling and psychosocial support to help manage feelings of uncertainty, fear and anxiety as other services being needed to be delivered before and after the intervention.

Indication(s) for the proposed medical service and clinical claim

The consultation feedback all strongly agreed with the proposed population, comparator, and clinical claims. One individual specified the importance of including all patients with cholangiocarcinoma, regardless of whether extra or intra hepatic disease as it can be very difficult to ascertain the correct site of origin of a cholangiocarcinoma.

Both individuals work in laboratories currently providing *IDH1* testing through next generation sequencing (NGS) for this population, with one individual supporting methodology agnostic testing as it would allow use of existing molecular testing and allow labs to acquire, validate, and have accredited a single gene polymerase chain reaction (PCR) test such as the Qiagen PCR test for *IDH1* hotspot variants.

Cost information for the proposed medical service

The consultation feedback strongly agreed with the proposed service descriptor, with one individual noting it is clear, succinct, unambiguous and in line with current item descriptors in use. The consultation feedback ranged from agreeing to strongly agreeing with the proposed service fee, noting it is in line with other single gene tests. Pancare noted that patients already experience high out-of-pocket expenses, and many patients are already self-funding the test.

Additional comments

The consultation feedback all noted that cholangiocarcinoma has a poor prognosis and that patients with this cancer are very sick, frequently unable to continue work and are paying for many additional costs to support their treatment including, dietary supplements, physiotherapy, psychological support, diagnostic testing and medication costs.

PASC noted that the public consultation responses were positive regarding the proposed population, comparator, and clinical claims.

Pathologist feedback strongly agreed on effectively using the diagnostic tissue samples and proceeding directly from histologically confirmation of CCA to molecular testing on their judgement.

Feedback was received that a negative test result may cause psychological distress. PASC discussed whether post-testing counselling will be needed for patients who have received negative test result. However, clinical expert opinion was that this is usually not needed, based on experience. PASC further noted that testing at diagnosis should reduce psychological distress from a negative result as it distances a possible negative test result from the time of relapse, thus giving the patient time to adapt to this result.

Next steps

PASC noted that the applicant has elected to progress its application as an Applicant Developed Assessment Report (ADAR).

Applicant Comments on Ratified PICO

The applicant had no comment.

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Appendix 1

The applicant provided the following reasons to justify palliative care/no treatment as the main comparator to ivosidenib:

CCA is a rare and aggressive cancer and 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). Current median survival at commencement of 1st line chemotherapy is 11.7 months (Valle et al 2010) and just 5.1 months following progression on 1st line chemotherapy (Zhu et al 2021).

For treating physicians and patients, the decision to initiate second-line chemotherapy is not straight forward. Whilst there are no data published on chemotherapy usage patterns for CCA in the Australian setting, the published literature from large real world cohort studies, as well as follow up of clinical trial participants shows between 57% and 82% of patients who received first-line chemotherapy do not go on to receive second-line chemotherapy (Table 4).

Table 3 Summary of proportion of patients receiving second-line therapy.

Publication	Proportion receiving 2 nd line chemotherapy n/N (%)
Valle et al 2010	72/410 (17.6%)
Cassier et al 2010	31/71 (43.6%)
Walter et al 2013	96/378 (25.4%)
Malka et al 2014	60/150 (40%)
Möhrling et al 2021	21/58 (36.2%)
Oh et al 2022	293/685 (42.7%)

Source: Servier Laboratories (Aust.) Pty.Ltd.

There are various reasons behind the choice to receive second-line chemotherapy; including age, fitness, response to first-line chemotherapy, predicted response and tolerability to second-line chemotherapy, prognosis, considerations regarding treatment burden (where expected survival is < 6 months), as well as patient preference.

Further there is no TGA-approved or PBS-listed second-line chemotherapy option available for the treatment of CCA. It is important to note the TGA—in granting ivosidenib priority determination in April 2022—agreed ivosidenib fulfilled the criteria, including criterion 3 which refers to the comparison against registered therapeutic goods, which specifies there are:

no therapeutic goods that are intended to treat, prevent or diagnose the condition are included in the Register (except in the part of the Register for goods known as provisionally registered goods);

The evidence supporting the use of FOLFOX as a second-line chemotherapy in CCA comes from the ABC-06 study. This trial was an open label RCT comparing FOLFOX to active symptom control (ASC) alone performed in sites in the UK. FOLFOX was administered every 2 weeks, consisting of oxaliplatin 85 mg/m², L-folinic acid 175 mg [or folinic acid 350 mg], fluorouracil 400 mg/m² [bolus], and fluorouracil 2400 mg/m² as a 46-h continuous intravenous infusion). No information on the patient's *IDH1* mutation status is published from the trial, therefore it is not possible to determine the effect of FOLFOX in this population.

Median follow up of the study was 27.1 months and showed FOLFOX improved median overall survival from 5.3 months to 6.2 months. Just 13 of the 81 patients (16%) randomised to FOLFOX completed all 12 cycles during the study. The main reasons for early discontinuation included radiological disease progression (24/81 patients), clinical disease progression (13/81 patients), intolerable toxicity (10/81 patients), intercurrent illness (5/81 patients), patient decision (5/81 patients), investigator decision (5/81 patients), or other unspecified reason (3/81 patients).

From a safety perspective, grade 3–5 adverse events reported in 42/81 (52%) patients in the ASC alone group and 56/81 (69%) in the ASC plus FOLFOX group, including three chemotherapy-related deaths (one each due to infection, acute kidney injury, and febrile neutropenia). The most frequently reported grade 3–5 FOLFOX-related adverse events were neutropenia (10/81 [12%] patients), fatigue or lethargy (9/81 [11%] patients), and infection (8/81 [10%] patients).

The European Society for Medical Oncology provided a benefit rating of 1 to FOLFOX as a second-line chemotherapy for CCA (the lowest clinical rating) .

In a more recent study, TOPAZ-1, published by Oh et al (2022) showed less than half (42.7%) of patients went on to receive second-line chemotherapy on progression following first-line chemotherapy treatment. As presented in the PICO set, due to the nature of clinical trials tending to enrol patients with better performance status and renal function compared to real world conditions, this proportion is expected to be at the upper end of the estimated use of FOLFOX in Australia yet is still below the threshold to declare it as the main comparator for ivosidenib in the 2nd line setting.

In summary the main comparator in both the 2nd line and 3rd line settings is nominated as palliative care/no active treatment, represented as placebo in the ClarIDHy study. This is supported by the literature where less than a third (573/1,752 [32.7%]) of patients across publications were fit enough to receive second-line chemotherapy following progression on first-line chemotherapy. FOLFOX is considered a secondary comparator in the 2nd line setting.

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