

# **MSAC Application 1779**

**Testing of tumour tissue to detect FGFR2 fusions or rearrangements in people with cholangiocarcinoma, to determine eligibility for treatment with PBS subsidised futibatinib**

**PICO Set**

## Population

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

This application requests Medicare Benefits Schedule (MBS) listing for testing to detect fibroblast growth factor receptor 2 (FGFR2) fusions or rearrangements in patients with locally advanced or metastatic cholangiocarcinoma (CCA), to determine Pharmaceutical Benefits Scheme (PBS) eligibility for futibatinib (Lytgobi).

Futibatinib is a potent and highly selective kinase inhibitor of FGFR 1-4 for patients who have locally advanced or metastatic CCA with an FGFR2 fusion or rearrangement and who have progressed following at least one prior line of systemic therapy. Futibatinib was granted orphan drug designation (ODD) and has been submitted for assessment by the Therapeutic Goods Administration (TGA).

Cholangiocarcinoma (CCA) is a heterogeneous group of neoplasms of the bile ducts and represents the second most common hepatic cancer after hepatocellular carcinoma (HCC) (Elvevi, Laffusa, Scaravaglio, Rossi, & Longarini, 2022). It has been reported as a rare disease in Western countries, accounting for <1% of all human cancers, and around 10-15% of all primary liver cancers. CCA is mostly diagnosed in the seventh decade of life with a small male predominance (male:female ratio of 1.2—1.5:1.0).

CCA is subclassified as (ESMO, 2023) (Elvevi, Laffusa, Scaravaglio, Rossi, & Longarini, 2022):

- intrahepatic CCA (iCCA), arising from bile ductules proximal to the second-order bile ducts, accounting for ~10%-20% of cases;
- perihilar CCA (pCCA), arising in the right and/or left hepatic duct and/or at their junction, accounting for ~50% of cases; and
- distal CCA (dCCA), arising from the epithelium distal to the insertion of the cystic duct, accounting for ~30%–40% of cases.

pCCA and dCCA collectively comprise extrahepatic CCA (eCCA).

The incidence of CCA in Australasia has been reported as 0.3 to 3.5 cases per 100,000 population and it is understood that CCA affects approximately 1,300 Australians each year (ESMO, 2023) (AGITG, 2023).

CCA still shows a high mortality rate due to its aggressiveness, late diagnosis, and immunoregulation capacity (Elvevi, Laffusa, Scaravaglio, Rossi, & Longarini, 2022). It is rarely diagnosed at an early stage owing to its silent clinical course, lack of biomarkers, difficult-to-access anatomical location, and highly desmoplastic and paucicellular nature.

CCA is associated with a dismal median overall survival (OS) of less than 12 months and a 5-year OS of less than 5% (Roth, et al., 2023). Patients with CCA commonly present with advanced disease; at diagnosis, 60-70% of patients have unresectable disease. When resection is possible, the 5-year OS is still low, varying between 15 and 40% for iCCAs, 8 and 47% for pCCAs and 20 and 54% for dCCAs.

The burden of CCA is steadily growing with increasing incidence worldwide and, despite advances in the understanding of CCA's pathogenetic mechanisms, there are limited therapeutic options available to patients and prognosis remains invariably poor.

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

MSAC 1779 - Testing of tumour tissue to detect FGFR2 fusions or rearrangements in people with cholangiocarcinoma, to determine eligibility for treatment with PBS subsidised futibatinib

Risk factors for CCA vary between regions and share chronic inflammation of the biliary epithelium as a key feature (ESMO, 2023). Patients with primary sclerosing cholangitis (PSC) in Western countries and those with hepatobiliary flukes or hepatolithiasis in Asian countries are at increased risk of pCCA. Cirrhosis and hepatotropic viruses are risk factors for iCCA, with odds ratios of 22.92 [95% confidence interval (CI) 18.24-28.79] for cirrhosis, 5.10 (95% CI 2.91-8.95) for hepatitis B virus (HBV) and 4.84 (95% CI 2.41-9.71) for hepatitis C virus (HCV), according to a recent meta-analysis. Recently, diabetes, obesity and use of hormonal contraceptives have been associated with an 81%, 62% and 62% increase in risk of iCCA, respectively.

An optimal care pathway, including diagnosis, staging and treatment planning, has been endorsed by the Australian Government and the Cancer Council (Cancer Council Victoria and Department of Health Victoria, 2021). The optimal care pathways describe the standard of care that should be available to all cancer patients treated in Australia including presentation, initial investigations, referral, and treatment, which consists of surgery, chemotherapy and systemic therapy and/or radiation.

CCAs are usually asymptomatic during early stages and early-stage CCA may only manifest as mild changes in serum liver function tests. Patients with iCCA, due to their often late presentation, are more likely to present with nonspecific symptoms such as fever, weight loss, and/or abdominal pain; symptoms of biliary obstruction are uncommon because these tumours do not necessarily involve the common hepatic/bile duct (NCCN 2023). Intrahepatic CCA may be detected incidentally as an isolated intrahepatic mass on imaging. In contrast, patients with extrahepatic CCA are likely to present with jaundice followed by evidence of a biliary obstruction or abnormality on subsequent imaging. In general, a diagnosis of CCA is usually based on the results of clinical examination of the abdomen, imaging scans using ultrasound, magnetic resonance imaging (MRI) or computed tomography (CT) and a biopsy, by a fine needle aspiration (FNA) or a core needle biopsy (CNB) (Pancare Foundation, N.D) (Rare Cancers Australia, 2023). Another option is an endoscopic retrograde cholangiopancreatography (ERCP) (Cancer Council NSW, 2020).

The prognosis of patients with advanced CAA is poor and the median survival for those undergoing supportive care alone is short. In patients presenting with locally advanced or metastatic disease, systemic chemotherapy remains the main palliative treatment option (Banales 2020). Historically, the first-line, standard of care treatment for patients with locally advanced or metastatic disease has been gemcitabine and cisplatin (Valle 2010) however based on the TOPAZ-1 study, cisplatin plus gemcitabine plus durvalumab is the new standard of care for advanced biliary cancer in the first-line setting.

Selection of subsequent-line systemic therapy for progressive disease depends on clinical factors including previous treatment regimen/agent, somatic molecular testing results, and extent of liver dysfunction. For patients who progress on first-line chemotherapy, FOLFOX combination therapy (folinic acid, 5-fluorouracil, and oxaliplatin) is the recommended subsequent-line chemotherapy in all-comers.

### FGFR2 fusions and rearrangements

Nearly 40% of patients with BTC harbour genetic alterations which are potential targets for precision medicine (ESMO, 2023). Therefore, guidelines recommend that molecular analysis should be carried out before or during first-line therapy to evaluate options for second and higher lines of treatment as early as possible in advanced disease (ESMO, 2023) (NCCN, 2023).

FGFR2 is a member of the FGFR family of receptor tyrosine kinases that activate a variety of downstream signalling cascades leading to cell proliferation and tumorigenesis (NCCN 2023). The FGFR family includes four receptor tyrosine kinases (RTKs), namely FGFR1 through FGFR4 (ESMO

MSAC 1779 - Testing of tumour tissue to detect FGFR2 fusions or rearrangements in people with cholangiocarcinoma, to determine eligibility for treatment with PBS subsidised futibatinib

2023). FGFR1-4 share a similar structural organisation. The activity of FGFRs is regulated by the 18-member family of secreted fibroblast growth factors (FGFs).

FGFR2 fusions or rearrangements occur in ~14% of patients with iCCA (Goyal, Meric-Bernstam, Hollebecque, Valle, & Morizane, 2023). FGFR2 fusions are generated by chromosomal rearrangements that fuse the C-terminal end of FGFR2 to heterologous sequences (ESMO 2023). In cancer, FGFR2 structural alterations (a) increase ligand affinity and therefore overcome restricted FGF availability, (b) cause ligand-independent FGFR2 dimerisation, and (c) disrupt the autoinhibited configuration of the FGFR kinase domain encoded by >100 fusion genes.

For CCA patients with FGFR2 fusions or rearrangements there is little information available regarding the treatment outcome of patients receiving chemotherapy. A retrospective analysis of 38 patients with advanced/metastatic CCA and tumours harbouring FGFR2 rearrangements (including fusions) receiving second-line treatment showed a median PFS of 4.4 months (95% CI: 3.0, 5.3) (Bibeau 2020), which is similar to the PFS reported for CCA patients overall receiving second-line chemotherapy (Lamarca 2014). Additionally, the ORR of 5.4% (95% CI: 0.7, 18.2) reported in another retrospective analysis of 71 CCA patients with FGFR2 rearrangements receiving second-line chemotherapy was not apparently different from the one for CCA patients overall receiving second-line chemotherapy regardless of genomic status (Javle 2020).

**Provide a rationale for the specifics of the eligible population:**

There are no reimbursed therapies specifically for the treatment of patients with locally advanced or metastatic CCA with FGFR2 fusions or rearrangements whose disease has progressed following systemic therapy, and response rates to standard of second-line chemotherapy care (preferred regimen = FOLFOX) are low. Given the overall poor outcomes associated with chemotherapy in this setting, there is an urgent need for patient access to novel targeted therapies.

Testing to detect FGFR2 fusions or rearrangements in patients with locally advanced or metastatic CCA will be used to determine PBS eligibility for futibatinib in patients who have locally advanced or metastatic CCA and who have progressed following at least one prior line of systemic therapy.

In FOENIX-CCA2, the pivotal study for futibatinib, the use of futibatinib in previously treated patients with FGFR2 fusion or rearrangement-positive locally advanced or metastatic CCA led to measurable clinical benefit. The use of futibatinib resulted in durable responses and survival that surpassed those indicated by historical data with chemotherapy, with an acceptable and monitorable safety profile.

**Are there any prerequisite tests?**

Yes, histological confirmation of CCA.

This is currently funded under MBS items 72823, 72824, 72825, 72826, and 72827.

**Are the prerequisite tests MBS funded?**

Yes

**Provide details to fund the prerequisite tests:**

N/A

## Intervention

**Name of the proposed health technology:**

*Test: FGFR2 fusion or rearrangement testing by next-generation sequencing (NGS) in tumour tissue sample.*

MSAC 1779 - Testing of tumour tissue to detect FGFR2 fusions or rearrangements in people with cholangiocarcinoma, to determine eligibility for treatment with PBS subsidised futibatinib

FGFR2 fusion or rearrangement testing by fluorescence in-situ hybridisation (FISH) in tumour tissue sample can also be considered as an option for testing likely to occur outside of centres with NGS capability.

In FOENIX-CCA2, FGFR2 fusion or rearrangement was prospectively identified by testing of tumour tissue at a central (66% of patients) or local laboratory (24% of patients) with the use of a 324-gene-panel assay (FoundationOne® CDx assay, Foundation Medicine) or by local testing of tumour tissue (7% of patients) or circulating tumour DNA (ctDNA) (3% of patients) (Goyal, Meric-Bernstam, Hollebecque, Valle, & Morizane, 2023).

FoundationOne CDx is a qualitative next-generation sequencing based in vitro diagnostic test that uses targeted high throughput hybridization-based capture technology for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumour mutational burden (TMB) using DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumour tissue specimens when using the DNAX extraction method. It is understood that testing is performed in the US. *The FoundationOne CDx assay is therefore nominated as the reference standard for this submission.*

Correlative research was also performed to assess the use of ctDNA profiling of plasma samples for the detection of *FGFR2* fusions and rearrangements. The partner-agnostic ctDNA platform used in the correlative analyses in this study identified *FGFR2* fusions or rearrangements in 87% of the patients evaluated.

For tissue-based testing, ESMO guidelines recommend that gene fusions involving *FGFR2* genes should preferably be interrogated at the RNA level using a panel-based method that can identify fusion transcripts of known and unknown fusion partners. Ideally, this approach should be combined with parallel DNA testing to identify break points which mainly involve exons 17 and 18 of *FGFR2*. Both DNA- and RNA-based NGS assays should ideally employ hybrid capture or anchored multiplex PCR technology.

NCCN guidelines recommend that both NGS assays, which include the *FGFR2* gene including its intronic regions, and break apart FISH assays, can be used to identify patients with *FGFR2* fusions/rearrangements in tumour tissue samples. As such, whilst the Applicant understands that NGS is the preferred methodology in clinical practice, *FGFR2* fusion or rearrangement testing by FISH in tumour tissue sample can also be considered as an option for testing likely to occur outside of centres with NGS capability.

Consideration could also be given to broadening the item descriptor to NGS testing for *FGFR1-4* fusions and rearrangements; this should have no impact on the complexity of the test.

The test results will serve to determine the patients' eligibility for treatment with PBS-subsidised futibatinib either when diagnosed with, or on progression to, locally advanced or metastatic CCA.

To allow for earlier planning for re-biopsy and a quicker transition to futibatinib for patients who have disease progression following untargeted anti-cancer treatment, testing is aimed to be delivered to all histologically confirmed CCA tissue at primary diagnosis of the cancer, regardless of stage or subtype. This is consistent with the Ratified PICO for Application 1750 - Testing of tumour tissue to detect *IDH1* variants in patients with cholangiocarcinoma to determine eligibility for ivosidenib on the PBS.

*Treatment: Futibatinib 20 mg orally daily until unacceptable toxicity or disease progression.*

MSAC 1779 - Testing of tumour tissue to detect FGFR2 fusions or rearrangements in people with cholangiocarcinoma, to determine eligibility for treatment with PBS subsidised futibatinib

Futibatinib is a highly selective, irreversible inhibitor of FGFR1-4. Unlike reversible ATP-competitive inhibitors, it forms a covalent adduct with a conserved cysteine residue in the FGFR kinase domain P-loop structure.

Futibatinib was granted orphan drug designation (ODD) and has been submitted for assessment by the Therapeutic Goods Administration (TGA).

**Describe the key components and clinical steps involved in delivering the proposed health technology:**

Next generation sequencing (NGS) is a high-throughput DNA and/or RNA sequencing method that facilitates the comprehensive genomic profiling of tumour tissue through their ability to identify four classes of genomic alterations: base substitutions (single nucleotide variants); insertions and deletions; copy number alterations; and gene fusions (rearrangements). NGS typically involves 4 steps: (1) Constructing the DNA library; (2) amplifying the library clonally; (3) sequencing the library, and (4) analysing data. NGS can be carried out on formalin-fixed and paraffin-embedded tumour tissue and is well suited for tissue biopsies. Alternatively, liquid biopsies using cell-free circulating DNA may be considered, if not enough tumour tissue is available for NGS.

FISH is a commonly used method for detecting chromosomal rearrangements, and has been effectively used to detect ALK, ROS1 and RET fusions in solid tumours. Break-apart probes can be used screen for FGFR2 fusions.

**Identify how the proposed technology achieves the intended patient outcomes:**

In FOENIX-CCA2, 42% of the patients who received futibatinib had a response, as determined by independent central review. The use of futibatinib resulted in durable responses and survival that surpassed those indicated by historical data with chemotherapy in patients with refractory intrahepatic cholangiocarcinoma, findings that led to an accelerated approval by the Food and Drug Administration for the use of this agent in patients with *FGFR2* fusion or rearrangement-positive intrahepatic cholangiocarcinoma.

Testing patients with CCA for FGFR2 fusion or rearrangement is expected to lead to a change in clinical management, as patients will be eligible to receive targeted treatment with futibatinib. This change is expected to lead to a significant improvement in clinical outcomes, as demonstrated by the pivotal FOENIX-CCA2 study.

**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 is aimed to be delivered to all histologically confirmed CCA tissue at primary diagnosis, regardless of stage or subtype. It is unlikely a patient would require more than one FGFR2 test over their lifetime.

MSAC 1779 - Testing of tumour tissue to detect FGFR2 fusions or rearrangements in people with cholangiocarcinoma, to determine eligibility for treatment with PBS subsidised futibatinib

**If applicable, advise which health professionals will be needed to provide the proposed health technology:**

Testing should be conducted and the results be interpreted and reported by a registered molecular pathologist in a National Association of Testing Authorities (NATA) accredited laboratory, which is validated to perform FGFR2 fusion or rearrangement testing.

**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 should be based on a referral 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 the detection of FGFR2 fusion or rearrangement using NGS would be conducted in a NATA-accredited laboratory using a validated test with the results interpreted and reported by a suitably qualified and trained pathologist.

**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

**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 healthcare system). This includes identifying healthcare resources that are needed to be delivered at the same time as the comparator service:**

*Test:* The nominated comparator is 'no testing'.

MSAC 1779 - Testing of tumour tissue to detect FGFR2 fusions or rearrangements in people with cholangiocarcinoma, to determine eligibility for treatment with PBS subsidised futibatinib

*Treatment:* Standard of care subsequent-line therapy, noting that guidelines (ESMO, NCCN) recommend FOLFOX as a preferred regimen for 'all comers'.

Application 1750 (Testing of tumour tissue to detect IDH1 mutations in patients with cholangiocarcinoma to determine eligibility for ivosidenib on the PBS) nominated palliative care as a primary comparator, which was accepted in the Ratified PICO. The sponsor would appreciate feedback from the PASC with regard to the relevance of palliative care for this application.

**List any existing MBS item numbers that are relevant for the nominated comparators:**

N/A

**Provide a rationale for why this is a comparator:**

*Test:* For patients with CCA, there is no molecular testing in the current clinical management pathway.

*Treatment:* Currently, there are no reimbursed therapies specifically for the treatment of patients with locally advanced or metastatic CCA with FGFR2 fusion or rearrangement whose disease has progressed following  $\geq 1$  line of prior systemic therapy. Aligned with clinical guidelines (ESMO, NCCN), these patients are likely to receive treatment regimens recommended for all-comers, with FOLFOX being the preferred option. Results from the randomised Phase 3 ABC-06 study showed that compared to active symptom control alone, active symptom control combined with FOLFOX in patients previously treated with combined cisplatin and gemcitabine improved median OS (6.2 vs. 5.3 months; adjusted HR, 0.69; P = .031) (NCCN, 2023).

**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?**

- 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 all)
- Full (subjects who receive the proposed intervention will not receive the comparator)

**Outline and explain the extent to which the current comparator is expected to be substituted:**

The proposed test will detect FGFR2 fusions or rearrangements in patients CCA, to determine PBS eligibility for futibatinib for patients who have locally advanced or metastatic CCA and who have progressed following at least one prior line of systemic therapy. Patients without FGFR2 fusion or rearrangement will continue to receive standard of care subsequent-line therapy.

## 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):**

- Health benefits
- Health harms
- Resources
- Value of knowing

*Test outcomes:*

Sensitivity, specificity, positivity predictive value (PPV), negative predictive value (NPV)



MSAC 1779 - Testing of tumour tissue to detect FGFR2 fusions or rearrangements in people with cholangiocarcinoma, to determine eligibility for treatment with PBS subsidised futibatinib

*Treatment outcomes:*

OS, PFS, ORR (study primary outcome), DOR, DCR, PROs, safety

*Health care system:*

Cost effectiveness of testing and treatment, financial implications

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

Testing patients with CCA for FGFR2 fusion or rearrangement is expected to lead to a change in clinical management, as patients with a positive result may be eligible to receive targeted treatment with PBS-subsidised futibatinib in 2L+. This change is expected to lead to a significant improvement in clinical outcomes, as demonstrated by the pivotal FOENIX-CCA2 study.

## Proposed MBS items

**How is the technology/service funded at present? (e.g., research funding; State-based funding; self-funded by patients; no funding or payments):**

Currently, any testing for FGFR2 fusion or rearrangement is self-funded by patients.

**Provide at least one proposed item with their descriptor and associated costs, for each Population/Intervention:**

Consideration could also be given to broadening the item descriptor to NGS testing for *FGFR1-4* fusions and rearrangements; this should have no impact on the complexity of the test.

MBS item number (where used as a template for the proposed item)	N/A
Category number	Category 6
Category description	Pathology Services
Proposed item descriptor	Next generation sequencing (NGS) test for FGFR2 fusion or rearrangement in tumour tissue from a patient with histologically confirmed locally advanced or metastatic cholangiocarcinoma, if: <ul style="list-style-type: none"> <li>the test is requested by a specialist or consultant physician to determine if requirements relating to FGFR2 fusion or rearrangement status for access to futibatinib under the Pharmaceutical Benefits Scheme are fulfilled.</li> </ul>
Proposed MBS fee	MBS fee to be confirmed, noting that the fee for item 73433 (NGS test for NTRK fusions) is \$1000.00.
Indicate the overall cost per patient of providing the proposed health technology	Overall cost to be confirmed in the integrated codependent submission
Please specify any anticipated out of pocket expenses	N/A
Provide any further details and explain	N/A

MSAC 1779 - Testing of tumour tissue to detect FGFR2 fusions or rearrangements in people with cholangiocarcinoma, to determine eligibility for treatment with PBS subsidised futibatinib

Fluorescence in-situ hybridisation (FISH) in tumour tissue sample can also be considered as an option for testing likely to occur outside of centres with NGS capability.

MBS item number (where used as a template for the proposed item)	N/A
Category number	Category 6
Category description	Pathology Services
Proposed item descriptor	Fluorescence in-situ hybridisation (FISH) test of tumour tissue from a patient with histologically confirmed locally advanced or metastatic cholangiocarcinoma, if: <ul style="list-style-type: none"> <li>the test is requested by a specialist or consultant physician to determine if requirements relating to FGFR2 fusion or rearrangement status for access to futibatinib under the Pharmaceutical Benefits Scheme are fulfilled.</li> </ul>
Proposed MBS fee	MBS fee to be confirmed, noting that the fee for item 73430 (FISH test for NTRK fusions) is \$400.00.
Indicate the overall cost per patient of providing the proposed health technology	Overall cost to be confirmed in the integrated codependent submission
Please specify any anticipated out of pocket expenses	N/A
Provide any further details and explain	N/A

## 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:**

Prior to being eligible for testing to detect FGFR2 fusion or rearrangement, patients will have been diagnosed with CCA.

Patients with a positive result may be eligible to receive targeted treatment with PBS-subsidised futibatinib in 2L+.

**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:**

N/A

### USE OF THE HEALTH TECHNOLOGY

**Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:**

Healthcare resources used in conjunction with testing for FGFR2 fusion or rearrangement include MBS item number 30694, for endoscopic ultrasound (endoscopy with ultrasound imaging), with or without biopsy, with fine needle aspiration for the diagnosis of pancreatic, biliary or gastric submucosal tumours.

If the presence of FGFR2 fusion or rearrangement is confirmed, the patient may be eligible for PBS-subsidised treatment with futibatinib.

**Explain what other healthcare resources are used in conjunction with the comparator health technology:**

The comparator is no test. Patients receiving standard of care subsequent-line therapy also receive a biopsy (MBS item number 30694) to confirm their diagnosis.

**Describe and explain any differences in the healthcare resources used in conjunction with the proposed health technology vs. the comparator health technology:**

There are no differences in healthcare resources used in conjunction with the proposed health technology vs. the comparator health technology.

**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:**

With the availability of FGFR2 fusion or rearrangement testing, patients with confirmed FGFR2 fusion or rearrangement may be eligible for PBS-reimbursed futibatinib treatment.

Patients may subsequently move between 2L+ treatment options for later lines of therapy, including moving to best supportive care.

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

The comparator is no test. Patients would likely receive untargeted standard of care for all-comers in 2L+.

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

Patients may subsequently move between 2L+ treatment options for later lines of therapy, including moving to best supportive care.

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

The following proposed clinical management algorithm (Figure 1) is adapted from the ESMO and NCCN Guidelines (ESMO, 2023) (NCCN, 2023), and considers the treatments that are currently available for this indication on the PBS.

By contrast, the current algorithm has no FGFR2 fusion or rearrangement testing and patients are treated with current standard of care therapies, regardless of FGFR2 fusion or rearrangement status.

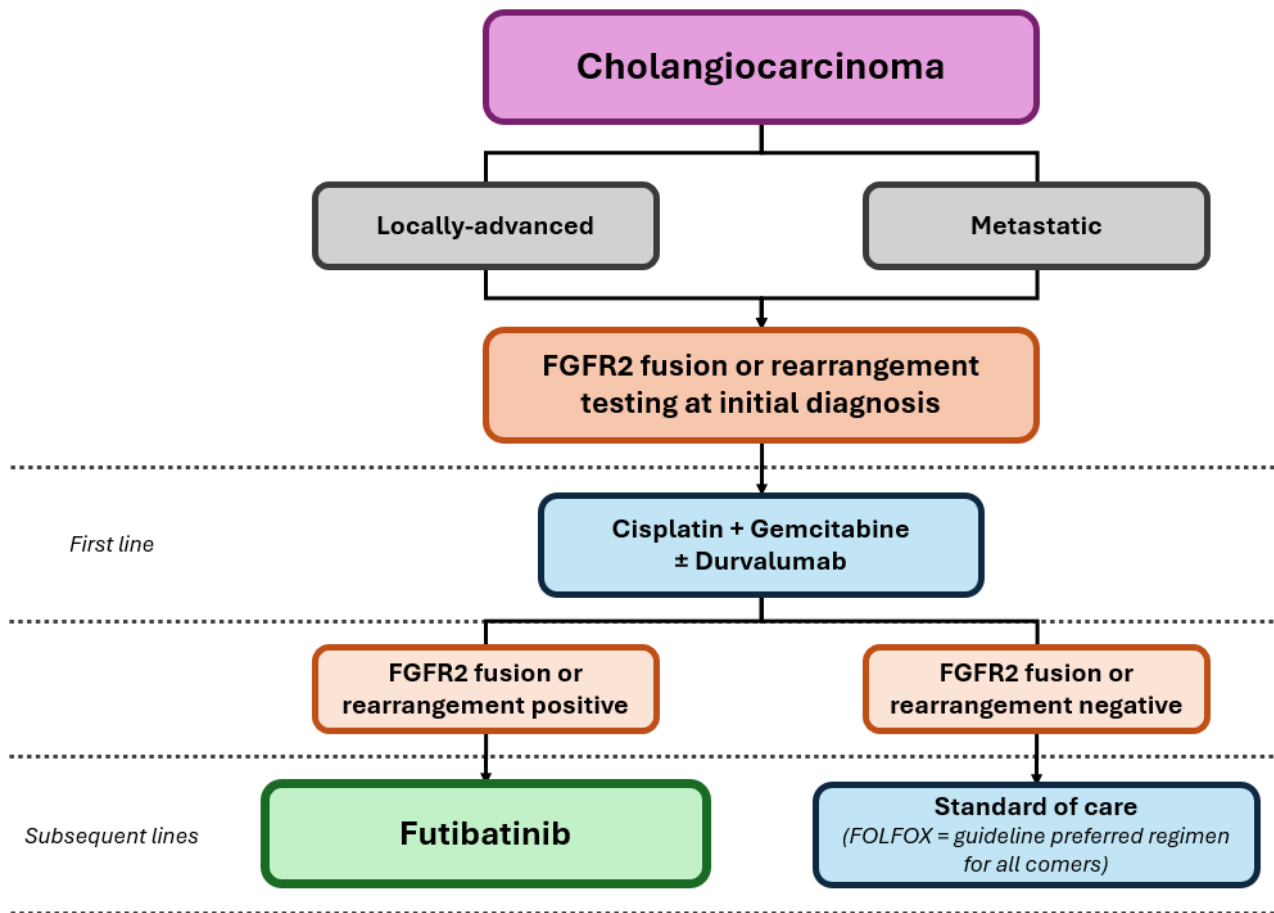


Figure 1: Proposed clinical management algorithm

## Claims

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

- Superior  
 Non-inferior  
 Inferior

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

Based on the results of FOENIX-CCA2, testing to detect FGFR2 fusion or rearrangement, followed by targeted therapy with futibatinib results in superior health outcomes compared to no testing and untargeted treatment/best supportive care in patients with locally advanced or metastatic CCA.

In FOENIX-CCA2, 42% of the patients who received futibatinib had a response, as determined by independent central review. The use of futibatinib resulted in durable responses and survival that surpassed those indicated by historical data with chemotherapy in patients with refractory CCA.

**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 a FGFR2 fusion or rearrangement may benefit from receiving a targeted treatment with futibatinib, rather than the current standard of care. This change is expected to lead to a significant improvement in clinical outcomes, as demonstrated by the pivotal FOENIX-CCA2 study.

MSAC 1779 - Testing of tumour tissue to detect FGFR2 fusions or rearrangements in people with cholangiocarcinoma, to determine eligibility for treatment with PBS subsidised futibatinib

**Identify how the proposed technology achieves the intended patient outcomes:**

Testing patients with CCA for FGFR2 fusion or rearrangement is expected to lead to a change in clinical management, as patients identified with a FGFR2 fusion or rearrangement will be eligible to receive targeted treatment with futibatinib.

**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:**

The PBS listing of futibatinib will result in the utilisation of FGFR2 fusion or rearrangement testing in patients with CCA.

Overall, the listing of the test and treatment on the MBS and PBS, respectively, is expected to be more costly than no testing + standard of care subsequent-line therapy.

## Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology. At 'Application Form lodgement',

	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.	Open-label, non-randomized study	Goyal, L et al. <i>Futibatinib for FGFR2-rearranged intrahepatic cholangiocarcinoma</i> FOENIX-CCA2, ClinicalTrials.gov number, NCT02052778	Patients (n=103) with unresectable or metastatic <i>FGFR2</i> fusion-positive or <i>FGFR2</i> rearrangement-positive iCCA and disease progression after $\geq 1$ previous lines of systemic therapy received futibatinib 20 mg once daily. The primary end point was OR, as assessed by independent central review. Secondary end points: response duration, PFS, OS safety, and PROs.	N Engl J Med 2023;388:228-39. DOI: 10.1056/NEJMoa2206834 <a href="https://pubmed.ncbi.nlm.nih.gov/36652354/">https://pubmed.ncbi.nlm.nih.gov/36652354/</a>	January 19, 2023

Identify yet-to-be-published research that may have results available in the near future (that could be relevant to your application).

No relevant published research identified for inclusion.

## References

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- Cancer Council NSW. (2020). *Bile duct cancer (cholangiocarcinoma)*. Retrieved from <https://www.cancercouncil.com.au/bile-duct-cancer/>
- Cancer Council Victoria and Department of Health Victoria. (2021). *Optimal care pathway for people with breast cancer: Second Edition*. Melbourne: Cancer Council Victoria. Retrieved March 12, 2024, from <https://www.cancer.org.au/assets/pdf/breast-cancer-optimal-cancer-care-pathway>
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