



**Australian Government**

**Medical Services Advisory Committee**

## **Public Summary Document**

### ***Application No. 1673 – Single operator, single use, peroral cholangiopancreatography for diagnosis of indeterminate biliary strictures and removal of difficult biliary stones***

**Applicant:** Boston Scientific Pty Ltd

**Date of MSAC Consideration:** 31 March – 1 April 2022

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

An application requesting Medicare Benefits Schedule (MBS) listing of single operator, single use, peroral cholangiopancreatography (POCPS) for diagnosis of indeterminate biliary strictures and removal of difficult biliary stones was received from the Boston Scientific Pty Ltd by the Department of Health.

#### **2. MSAC's advice to the Minister**

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported the creation of new Medicare Benefits Schedule (MBS) items for peroral cholangiopancreatography (POCPS) for diagnosis of indeterminate biliary strictures and removal of difficult biliary stones. MSAC noted limitations in the clinical evidence but considered POCPS was likely to have superior effectiveness and non-inferior safety compared with repeat use of endoscopic retrograde cholangiopancreatography for both the diagnostic and therapeutic intervention populations. MSAC considered POCPS has non-inferior effectiveness compared with laparoscopic choledochotomy for the removal of difficult biliary stones. MSAC considered that POCPS had uncertain but acceptable cost effectiveness and would result in a small increase in cost to the MBS.

#### **Consumer summary**

MSAC noted that this is an application from Boston Scientific requesting Medicare Benefits Schedule (MBS) listing of single operator, single use peroral cholangiopancreatography (POCPS) for diagnosing indeterminate biliary strictures and removing difficult biliary stones.

Biliary strictures occur when the bile duct (the tube that carries bile from the liver to the small intestine) becomes too narrow or blocked. This can be caused by conditions such as inflammation in the bile ducts, biliary stones (also known as gallstones) and a rare type of cancer. Bile is a substance that helps the body digest fat in food. When the bile duct becomes narrow or blocked, bile backs up, causing symptoms like jaundice and, potentially, low-grade sepsis (when the body reacts to an infection, which causes damage to its own organs).

### **Consumer summary**

Techniques to diagnose narrowing of the bile duct (biliary strictures) often involve a procedure called endoscopic retrograde cholangiopancreatography (ERCP). ERCP combines X-ray and an endoscope (a long, flexible tube with a light and camera on the end) to inject contrast into the bile and pancreatic ducts. It is not always possible to make a diagnosis of a condition causing the narrowing of the bile duct (biliary strictures) using ERCP. But if a condition that may cause cancer is suspected, patients will sometimes undergo surgery, even if the narrowing or blockage actually turns out to be benign (non-cancerous). Biliary stones can usually be removed during ERCP, but some cannot be removed because they are too large or stuck behind a narrowing of the bile duct. This can lead to negative patient outcomes, such as longer procedure times, multiple ERCP procedures and surgery.

Peroral cholangiopancreatography (POCPS) can be used during an ERCP procedure. POCPS uses a small, high-definition scope that can go directly into biliary and pancreatic ducts. Because POCPS produces clear images of the inside of ducts, it can allow for a more accurate diagnosis of narrowing of the bile duct (biliary strictures) and make it easier for doctors to remove stones that are large or hard to remove (called “difficult stones”).

For diagnosing the cause of narrowing of a bile duct (biliary strictures) and removing difficult stones, MSAC considered POCPS to be at least as safe as, and more effective than, ERCP. MSAC also considered POCPS was at least as effective as surgery for removing difficult biliary stones. MSAC considered there would only be a small increase in the cost to the MBS.

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

MSAC supported POCPS for diagnosing indeterminate biliary strictures (narrowing of the bile duct) and removing difficult biliary stones. MSAC noted the limitations in the clinical evidence, but considered POCPS was more effective and as safe as ERCP for diagnosing the cause of narrowed bile ducts (biliary strictures) and removing difficult stones, and as effective as surgery for removing difficult stones. MSAC also considered that POCPS was good value for money, and would result in only a small increase in cost to the MBS.

### **3. Summary of consideration and rationale for MSAC’s advice**

MSAC noted that this application from Boston Scientific is for Medical Benefits Schedule (MBS) listing of single operator, single use peroral cholangiopancreatography (POCPS) for diagnosing indeterminate biliary strictures and removing difficult biliary stones. MSAC noted that POCPS is currently only available in a limited number of public tertiary institutions, so MBS funding would make the service available to the private sector.

MSAC noted this application proposed two new MBS listings of single-operator, single-use POCPS for:

- diagnosis of indeterminate biliary strictures following unsuccessful endoscopic retrograde cholangiopancreatography (ERCP)-guided brush cytology and/or intraductal biopsy
- POCPS-guided electrohydraulic/laser lithotripsy for therapeutic removal of difficult biliary stones following unsuccessful ERCP-guided balloon/basket and/or lithotripsy with sphincterotomy.

MSAC noted consumer feedback was generally supportive of this application, but feedback noted the importance of training and credentialing practitioners in the use of POCPS. The Gastroenterological Society of Australia was supportive of the application but recommended a minimum case load of 10 cases per year for operator credentialing. The society also stated that

the Conjoint Committee for the Recognition of Training in Gastrointestinal Endoscopy specifies requirements for recognition of training in endoscopy and that this should be a requirement for POCPS. Both MSAC and the applicant agreed that only trained experienced operators should use POCPS. MSAC advised the Department that the credentialing requirement should be added to the explanatory notes for the items. MSAC also questioned whether in experienced hands, POCPS might replace ERCP as first-line treatment for difficult biliary stones. However, MSAC agreed failed ERCP will be a pre-requisite for POCPS.

MSAC noted the clinical need for POCPS, including:

- diagnosis of biliary strictures that may have uncertain aetiology and risk-prediction following imaging, pathology, and ERCP-guided cytology and biopsy
- surveillance of patients with primary sclerosing cholangitis (PSC); as these patients are recommended to have annual screening given the known increased risk for cholangiocarcinoma and may require liver transplantation
- the early diagnosis of cholangiocarcinoma requiring liver or pancreatic resection
- use in patients who have failed ERCP-guided balloon/basket biliary stone retrieval or lithotripsy who are unfit for laparoscopy.

MSAC noted the following MBS item descriptors to be mostly appropriate but advised that “difficult” biliary stones should be defined as stones proximal to a stricture, or stones that are greater than 10mm diameter. MSAC acknowledged that the pre-MSAC response agreed with limitations on the item descriptor as suggested by ESC; namely, to include the multiple operation rule in the item descriptors. MSAC advised that a benefit for surgical assistance is not needed as ERCP procedures are generally performed by a single clinician with nursing assistance. MSAC advised that other diagnostic imaging items could be restricted from being claimed on the same occasion as imaging procedures would have been performed earlier. MSAC also advised that co-claiming associated procedures such as sphincterotomy and extraction of biliary tract calculus should be restricted.

MSAC noted that PASC advised limiting the number of repeat procedures to two per year for the diagnostic use and three per year for the therapeutic use. However, MSAC recommended limiting the therapeutic use to a maximum of two procedures per treatment cycle as patients with recurrent biliary stones have a high incidence of further recurrence and surgical removal and bile duct drainage is the better long-term option. MSAC advised limiting the diagnostic use to two procedures over one year unless PSC is confirmed – in this case, the limit should be a maximum of three procedures per year ongoing to accommodate screening of PSC patients for cholangiocarcinoma.

This would allow the uptake, number of repeat procedures, long-term safety and so on to be monitored and compared to ERCP; the listing could then be reviewed in the future.

MSAC noted that the fee was \$618.91 for diagnostic use and \$865.72 for therapeutic use (with the fee being higher for the therapeutic use because it takes longer than the diagnostic procedure); these are 160% and 228% the cost of ERCP alone (based on MBS item 30484). MSAC acknowledged the applicant’s claim that the difference in fee compared to ERCP is because POCPS is more technically demanding (as stated by the National Institute for Health and

Care Excellence 2015<sup>1</sup>) and takes up to 50% longer. MSAC considered a higher fee for POCPS (compared with ERCP) was justified. MSAC considered the fee for the diagnostic item may be appropriate. However, MSAC considered the fee for the therapeutic application was not appropriate and questioned if the fee for the therapeutic use should be the same as that for endoscopic sphincterotomy with or without extraction of biliary stones (\$586.15, from MBS item 30485).

MSAC noted POCPS also has several costs associated with it, including \$redacted for the cost of the digital controller, \$redacted for the cost of consumables for the diagnostic use, and \$redacted for the cost of consumables for the therapeutic use (including \$redacted for a disposable miniscope). MSAC also noted the bulk billing rate for ERCP is low (16.8%). Despite this, MSAC noted the pre-MSAC response that there would be minimal out-of-pocket costs for patients, as capital/consumable costs would be absorbed by hospital/private health insurance. MSAC advised that for funding purposes, POCPS should be restricted to provision in hospital settings and may be undertaken as a day procedure. MSAC noted that POCPS would reduce the impact on public funding by moving patients to the private sector.

MSAC considered repeat ERCP-guided cytology and biopsy to be appropriate comparators for the diagnostic use of POCPS, but noted the frequency of repeat procedures was not specified. MSAC also noted that in the absence of POCPS, surgery was often the definitive method of making or refuting a diagnosis of malignancy (and concomitant treatment if malignancy present), and considered the quoted mortality rates of surgery in the application to be overstated. MSAC also considered laparoscopic choledochotomy to be an appropriate comparator for the therapeutic use of POCPS, noting that surgical clearance of stones in the biliary tree is definitive when there have been previous recurrences of primary duct stones (18% chance of recurrence).

MSAC considered the scientific evidence to be limited, including small patient numbers in studies, some studies having a high risk of bias, and the evidence not always including patients who had first-line ERCP (which is the proposed population for the PICO). MSAC noted the reference standard for investigative use was inconsistently applied in the direct comparative studies. MSAC considered the supportive evidence in the form of naïve indirect comparisons had several methodological deficiencies. However, MSAC noted that the evidence did suggest that POCPS has a clinical place for both stricture diagnosis and difficult stone removal.

MSAC noted that it was difficult to establish the comparative safety for either the diagnostic or therapeutic use. The numbers of patients in the studies were very small, making it difficult to determine rates of adverse events such as cholangitis and pancreatitis, and there was no systematic collection of harms. While MSAC considered there was a need for further evidence to establish the safety of POCPS, it considered the evidence did suggest that POCPS had non-inferior safety compared to ERCP, and at least non-inferior (potentially superior) safety compared to choledochotomy.

Regarding clinical effectiveness, MSAC noted that when experts perform POCPS for diagnostic use, it appeared to have superior sensitivity compared to ERCP-guided biopsy (68–77% versus 22–29%) and cytology (77% versus 6%) and resulted in fewer indeterminate results. MSAC considered the estimates to be uncertain due to the limitations in the clinical evidence.

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<sup>1</sup> National Institute for Health and Care Excellence (2015). The SpyGlass direct visualisation system for diagnostic and therapeutic procedures during endoscopy of the biliary system. <https://www.nice.org.uk/advice/mib21/resources/the-spyglass-direct-visualisation-system-for-diagnostic-and-therapeutic-procedures-during-endoscopy-of-the-biliary-system-pdf-63499040090053>.

For complete stone clearance, MSAC noted that expert-performed POCPS is superior compared to ERCP-guided balloon/basket stone removal and/or lithotripsy (92% success rate versus 62%), and is non-inferior compared to choledochotomy (96% success rate). In terms of health outcomes, MSAC noted that POCPS results in probable earlier definitive diagnosis and reduced unnecessary surgery and repeat ERCP for both therapeutic and diagnostic uses.

For the economic evaluation, MSAC noted that a cost-effectiveness analysis (CEA) was used for both the diagnostic and therapeutic uses. MSAC noted that for the diagnostic use, the CEA assumed superior effectiveness and non-inferior safety for POCPS. MSAC noted that incremental cost-effectiveness ratio (ICER) per correct diagnosis was \$5,949 including hospital costs. POCPS had a dominant ICER when a terminal care cost was applied to all patients with malignant strictures diagnosed as benign. MSAC considered the ICER to be uncertain due to the uncertainty in the clinical inputs. MSAC noted other key drivers of the ICER were the diagnostic performance of POCPS, reduction of downstream procedures, the cost of terminal care for missed malignancy. MSAC noted the CEA for the therapeutic use the CEA assumed superior effectiveness and non-inferior safety versus ERCP, but non-inferior effectiveness and superior safety versus choledochotomy. POCPS had a dominant ICER per successful stone removal in the base case and the additional analyses presented in the ESC report.

However, MSAC considered this to be uncertain as the magnitude of savings depends on the degree that POCPS replaces choledochotomy and avoids repeat ERCP.

MSAC noted that the estimated number of POCPS services, from year 1 to year 6, are 29–135 for the diagnostic use, and 78–359 for the therapeutic use. MSAC noted the financial estimates were affected by the MBS fee, number of repeat procedures, and uptake predictions. MSAC considered the estimated net costs to the MBS to be minimal: \$2,596 in year 6 for the diagnostic use, and \$8,194 in year 6 for the therapeutic use. MSAC noted that capital and consumable costs were attributed to hospitalisation costs that would be paid by health insurance in the private sector. However, MSAC considered that it was likely that patients would incur out-of-pocket costs.

MSAC supported creating new MBS items for POCPS for diagnosis of indeterminate biliary strictures and removal of difficult biliary stones. MSAC acknowledged the limitations in the clinical evidence, but considered it was difficult to establish better direct comparative evidence. Based on the available evidence, MSAC considered that POCPS was likely to have superior effectiveness and non-inferior safety compared with repeat ERCP for both diagnostic and therapeutic purposes. MSAC also considered POCPS has non-inferior effectiveness and at least non-inferior safety compared with laparoscopic choledochotomy for the removal of difficult biliary stones. MSAC also considered there to be an unmet clinical need for POCPS. MSAC considered that although no evidence was presented, the use in PSC was supported due to the high unmet clinical need in this group of patients. MSAC considered that POCPS likely had acceptable cost-effectiveness and would result in a small increase in cost to the MBS.

MSAC advised that the item descriptor could define difficult biliary stones as those greater than 10 mm in size or lying above a stricture which have failed prior ERCP. MSAC advised that the explanatory notes for the items should outline the appropriate credentialing requirements for proceduralists and institutions (as applies for TAVI). MSAC requested the Department review the utilisation and credentialing of POCPS after one year of MBS listing and compare the utilisation of POCPS with repeated ERCP.

## 4. Background

MSAC has not previously considered POCPS for the diagnosis of indeterminate biliary strictures or for the removal of difficult biliary stones.

## 5. Prerequisites to implementation of any funding advice

The proposed technology has been listed in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (Table 1)

There are no prerequisites to the implementation of any funding for POCPS.

**Table 1 TGA registered POCPS devices and accessories used for the diagnosis of indeterminate strictures and removal of difficult bile stones**

Population	ARTG number	Approval date	Manufacturer	Product name
Both	236205 <sup>b</sup>	14/04/2015	Boston Scientific Corporation	Flexible video choledochoscope
	335180 <sup>a</sup>	25/04/2020	Boston Scientific Corporation	Light source/processing unit, endoscope
Indeterminate biliary strictures	137089 <sup>b</sup>	2/04/2007	Boston Scientific Corporation	Endoscopic forceps, biopsy, flexible
Difficult biliary stones	290522 <sup>b</sup>	21/06/2017	Northgate Technologies Inc (Nortech)	Lithotripter, internal, electrohydraulic
	290314 <sup>c</sup>	16/06/2017	Northgate Technologies Inc (Nortech)	Lithotripter, internal, electrohydraulic
	320152 <sup>b</sup>	15/07/2019	Boston Scientific Corporation	Urogenital surgical laser system beam guide, single use
	287772 <sup>c</sup>	11/04/2017	Boston Scientific Corporation	Surgical Ho:YAG-laser system

a Medical device class I

b Medical device class IIa

c Medical device class IIb

Source: <https://www.ebs.tga.gov.au/>, accessed February 2021

It is noted in Application 1072 that Australia is limited by the availability of endoscopic ultrasound equipment and the number of technically trained experts. The applicant has not discussed the current supply of equipment and accredited endoscopic retrograde cholangiopancreatography (ERCP) proceduralists available to perform peroral cholangiopancreatography (POCPS) in the ADAR. This is worth considering for the future dissemination of the procedure.

## 6. Proposal for public funding

The proposal for public funding (updated based on the pre-ESC response) is listed in Table 2 and Table 3. The proposed technologies are new; and the proposal intends to create new MBS items.

**Table 2 Proposed MBS item for POCPS for difficult biliary stones: therapeutic application**

Category 3 – Therapeutic procedures
<p>MBS item *XXXX</p> <p>Single operator, single use peroral cholangiopancreatography (POCPS) guided electrohydraulic/laser lithotripsy for removal of difficult bile stones, that have failed at least one attempt at removal via conventional ERCP extraction techniques, during an endoscopic retrograde cholangiopancreatography (ERCP) procedure, not being a service to which item 30484 is applied.</p> <p>A maximum of three procedures per year.</p> <p>Multiple Operations Rule.</p> <p>(Anaes.)</p>
Fee: \$865.72 Benefit: 75% = \$649.29

**Table 3 Proposed MBS item for POCPS for indeterminate biliary strictures: investigative application**

Category 5 – Diagnostic imaging services
<p>MBS item *XXXX</p> <p>Single operator, single use peroral cholangiopancreatography (POCPS) with biopsy, for the diagnosis of indeterminate biliary strictures, defined as strictures with indeterminate results from conventional diagnostic ERCP guided brush cytology and/or intraductal biopsy, during an endoscopic retrograde cholangiopancreatography procedure, not being a service to which item 30484 is applied.</p> <p>A maximum of two procedures per year.</p> <p>(Anaes.)</p> <p>Multiple operations rule.</p>
Fee: \$618.91 Benefit: 75% = \$464.18

The procedure is intended to be performed by a specialist skilled in endoscopic retrograde cholangiopancreatography (ERCP; most commonly a gastroenterologist or surgical endoscopist). Consistent with the [Ratified PICO](#) (p20, Application 1673), the service is not restricted to any centre or a particular specialist group.

The proposed fee represents 228% of existing MBS fee for ERCP (item 30484) for the therapeutic application and 163% of this MBS fee for the investigative application. PASC requested further justification for the proposed MBS fees but this was not provided in the ADAR. The ADAR referenced the Alberta Health Services reimbursement fees and a study by Sandha et al. (2018), however, the basis for these claims could not be verified in the referenced publication. The applicant’s pre-ESC response emphasised that its advisory board confirmed the greater procedural complexity of POCPS compared to standard ERCP. A list of complexity levels for ERCP by the American Society for Gastrointestinal Endoscopy (ASGE) was provided (Sahar 2019).

The pre-MSAC response provided further rationale for the fee. This included:

- Reiterating that POCPS has increased procedural complexity compared to standard ERCP. The pre-MSAC response considered that this was supported by clinical guidelines, consensus statements, classifications for ERCP procedures, and consultation feedback.
- MBS items for urological procedures have higher reimbursement for direct visualisation in combination with biopsy or EHL/LL.

The ADAR omitted components of the MBS item descriptor in the Ratified PICO. The pre-ESC response confirmed the criteria agreed upon in the Ratified PICO and accepted the amendments suggested in the commentary including adding the Multiple Operation Rule, a maximum of three procedures in any 12-month period for therapeutic POCPS and a maximum of two procedures in any 12-month period for diagnostic POCPS. In the Ratified PICO, PASC agreed to a limit of two POCPS per year for indeterminate biliary strictures as this will allow for repeat POCPS for ongoing surveillance of primary sclerosing cholangitis (PSC) patients who have a high risk of cholangiocarcinoma. For difficult biliary stones, PASC determined that a maximum of three procedures per year will be allowed because the implication to the patient if the stone is not removed is that they will require surgery.

PASC expressed concerns about large out-of-pocket costs incurred by the patients with the inclusion of consumables and disposables considered for each procedure. The ADAR considered the cost of capital equipment and consumables are expected to primarily be funded by private health insurers. The commentary noted that although there were incremental cost savings per patient with POCPS for both applications (therapeutic and investigative), the commentary considered that the per patient out-of-pocket costs are likely to be larger with the inclusion of capital, consumables, and additional hospital costs. The largest difference in cost with the inclusion of capital equipment and consumables between the intervention and comparator arms is the inclusion of SpyGlass equipment, where the SpyGlass DS II Catheter is \$2,500 alone (which is not required in the ERCP procedure). The pre-ESC response reaffirmed that the costs of consumables and capital equipment are absorbed by the hospital budgets, with minimal out-of-pocket costs incurred by patients.

ESC noted that there were differences in the capital and consumable equipment outlined in the ADAR, the SpyGlass Brochure, and the American Society for Gastrointestinal Endoscopy (ASGE) Technology Committee's 2016 Status Evaluation Report on cholangiopancreatography (Table 4). ESC noted that there were updates to the technology in 2018 which could account for the differences. This was addressed in the applicant's pre-MSAC response.

**Table 4: Capital equipment and consumables for POCPS**

Item <sup>a</sup>	ADAR	SpyGlass Brochure	ASGE 2016
SpyGlass DS Digital Controller	Yes	Yes	Yes
Autolith Generator	Yes	Yes	Yes <sup>b</sup>
SpyGlass DS II catheter	Yes	Yes (2 versions)	Yes
Autolith EHL probe / laser fibre	Yes	Yes	Yes <sup>b</sup>
SpyBite Max biopsy forcep	Yes	Yes	Yes
SpyGlass Retrieval Basket	No (optional, rarely used)	Yes	No
SpyGlass Retrieval Snare	No (optional, rarely used)	Yes	No
Autolith Touch Extender Cable	Yes	Yes	No
Autolith Touch Foot Pedal		Yes	Yes (with irrigation pump)
Travel cart	No	No	Yes
Light source	No	No	Yes
Video monitor	No	No	Yes
Irrigation pump	No	No	Yes
Ocular piece	No	No	Yes
Isolation transformer	No	No	Yes
Storage tray	No	No	Yes

Source: ADAR Economics and Financial Estimates spreadsheets, [SpyGlass DS System Brochure](#), and the ASGE Technology Committee's [2016 Status Evaluation Report on Cholangiopancreatography](#); and applicant's pre-MSAC response

Abbreviations: ASGE = American Society for Gastrointestinal Endoscopy; ERCP = endoscopic retrograde cholangiopancreatography; POCPS = peroral cholangiopancreatography.

<sup>a</sup> Excluded consumables also used for ERCP

<sup>b</sup> Not specifically for Spyglass

## 7. Population

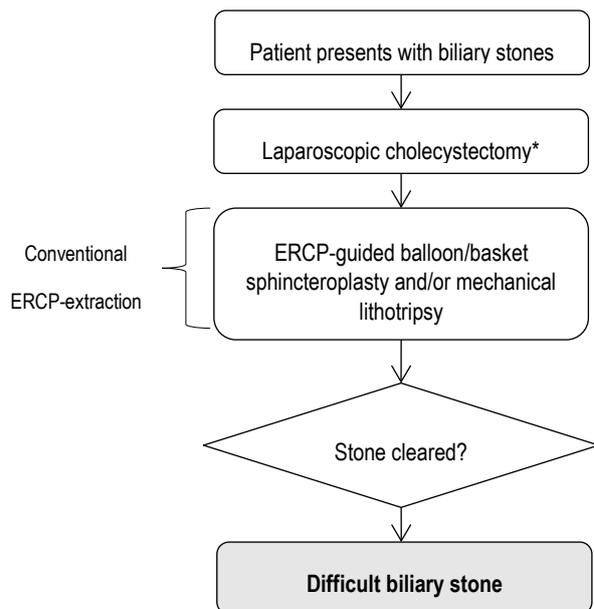
There are two PICO sets defined in the ADAR: one for the therapeutic application (POCPS-guided laser lithotripsy (LL) or POCPS-guided electrohydraulic lithotripsy (EHL) for the removal of difficult biliary stones) and one for the investigative application (POCPS-guided visualisation and biopsy for the diagnosis of indeterminate biliary strictures).

### Therapeutic application

The population proposed as eligible for therapeutic POCPS are patients with difficult biliary stones, defined as unsuccessful clearance of stone(s) by conventional ERCP extraction techniques (ERCP-guided balloon/basket sphincteroplasty and/or mechanical lithotripsy).

The proposed technology would be used in conjunction with the current technology (ERCP) when extraction using conventional extraction techniques fails. The ERCP component of the current technology is publicly funded by the MBS (item 30484). In case ERCP-guided balloon/basket sphincteroplasty fails to remove the stone, mechanical lithotripsy may be used during the same ERCP procedure. This component of the procedure is not listed on the MBS, and currently hospitals absorb the costs.

The patient's clinical management pathway before they are eligible for POCPS-guided LL or EHL is summarised in Figure 1.



**Figure 1 Clinical management pathway before patients are eligible for therapeutic POCPS**

Abbreviations: EPBD=endoscopic papillary balloon dilation; ERCP=endoscopic retrograde cholangiopancreatography; ES=endoscopic sphincterotomy

\* Laparoscopic cholecystectomy may be done, prior to or following an ERCP procedure.

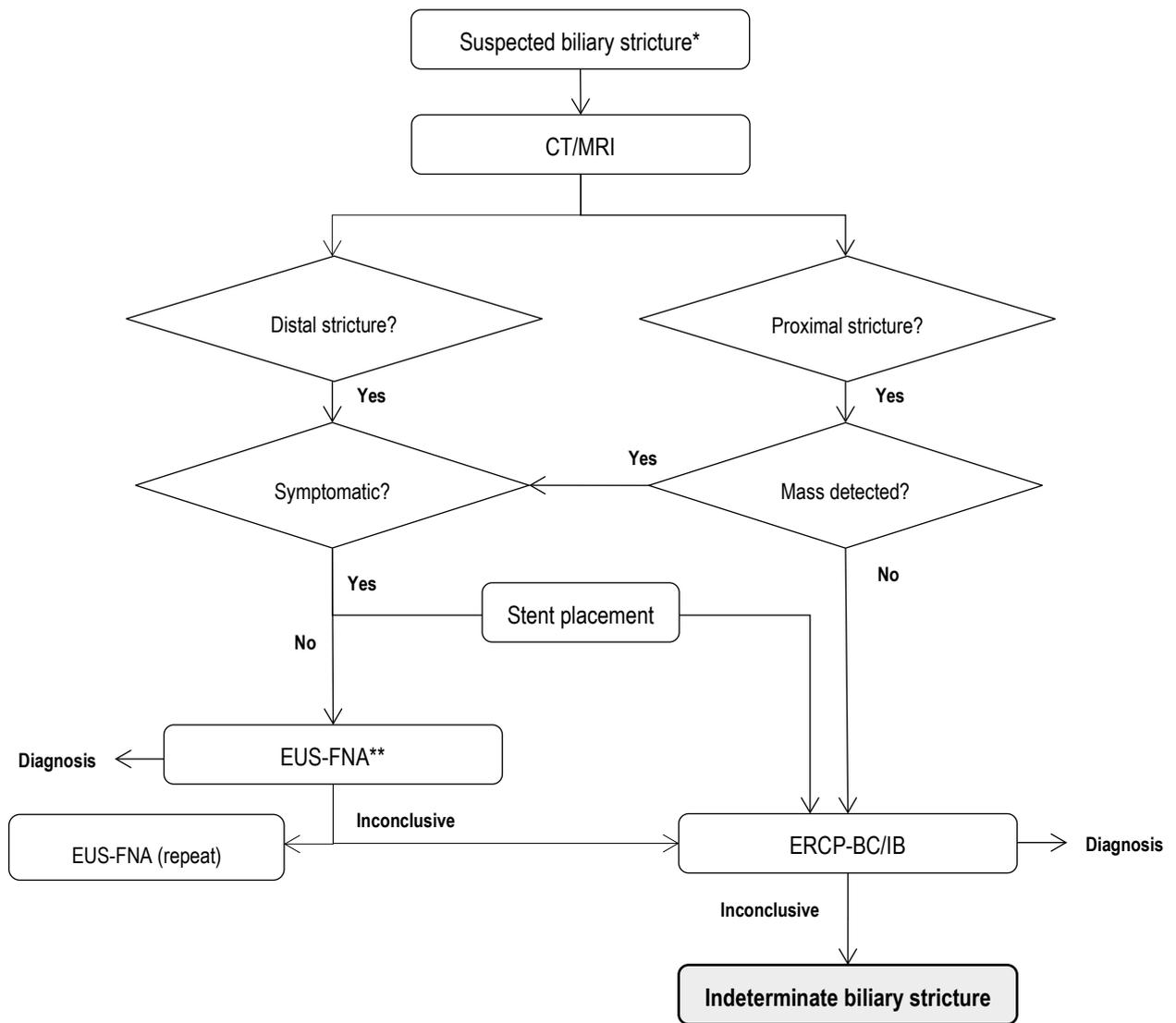
The ADAR claims that the higher procedural success of POCPS-guided LL/EHL will help avoid repeated unsuccessful ERCP procedures or laparoscopic choledochotomy, a more invasive surgical extraction with prolonged hospitalisation.

### Investigative application

The population proposed as eligible for investigative POCPS visualisation and biopsy are patients with inconclusive biliary strictures (i.e., inability to make a diagnosis) from prior ERCP-guided brush cytology and/or ERCP-guided intraductal biopsy.

The proposed technology would be used in conjunction with the current technology (ERCP) when prior ERCP-guided attempts failed to reach a definitive diagnosis. The ERCP component of the current technology is publicly funded by the MBS (item 30484).

The patient's clinical management pathway before they are eligible for POCPS-guided visualisation and biopsy is summarised in Figure 2.



**Figure 2 Clinical management pathway before patients are eligible for diagnostic POCPS**

Abbreviations: CT=computerized tomography; ERCP-BC/IB=endoscopic retrograde cholangiopancreatography-guided brush cytology and/or intraductal biopsy, EUS-FNA=endoscopic ultrasound with fine needle aspiration; MRI=magnetic resonance imaging, POCPS=single use, single operator peroral cholangiopancreatography

\* Patients with suspected biliary stricture typically present with cholestatic clinical patterns including abdominal pain, nausea, fatigue, pruritus, dark urine, light stool, jaundice and/or abnormal liver tests (elevated alkaline phosphatase and bilirubin levels).

\*\* EUS-FNA considered only after taking into consideration risk of tumour seeding

The ADAR addressed the requirements of the Ratified PICO.

## 8. Comparator

### Therapeutic application

In the absence of POCPS, patients with difficult biliary stones may receive one of two procedures. This choice is dependent on the preference of the treating physician.

1. ERCP-guided mechanical lithotripsy (MBS item 30484 for the ERCP component, Table 5). Mechanical lithotripsy is not listed on the MBS, and currently hospitals absorb the costs of this component of the procedure.
2. Laparoscopic choledochotomy (MBS item 30454 for choledochotomy; Table 6).

**Table 5 MBS item for ERCP**

Category 3 - Therapeutic Procedures
MBS item 30484 ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY Multiple Operation Rule (Anaes.) Fee: \$379.70 Benefit: 75% = \$284.80 85% = \$322.75 (See para TN.8.17 of explanatory notes to this Category)

**Table 6 MBS item for laparoscopic choledochotomy**

Category 3 - Therapeutic Procedures
MBS item 30454 Choledochotomy without cholecystectomy, with or without removal of calculi Multiple Operation Rule (Anaes.) (Assist.) Fee: \$1,371.65 Benefit: 75% = \$1,028.75

As stated in the Ratified PICO, item 30457 (choledochotomy, intrahepatic, involving removal of intrahepatic bile duct calculi) is also considered an appropriate MBS item for patients with intrahepatic stones. As the majority of the population receiving laparoscopic choledochotomy are treated for extrahepatic stones, item 30454 has been used throughout this ADAR. The cost of item 30457 has been considered in a sensitivity analysis. The commentary considered that this was appropriate.

### **Investigative application**

In the absence of POCPS, patients with indeterminate biliary strictures will undertake radiologically guided ERCP with brush cytology and/or blind intraductal biopsy (MBS item 30484; Table 5).

## **9. Summary of public consultation input**

### **Therapeutic application**

The Department received targeted consultation feedback from the Gastroenterological Society of Australia (GESA) and from a health professional.

GESA was strongly supportive of the application and considered that POCPS is superior to standard ERCP-based techniques for the removal of difficult biliary stones. Increased availability of POCPS through MBS funding would reduce the number of procedures patients undergo therapeutically, such as multiple ERCP procedures with attempted extraction of stones using standard transpapillary techniques or therapy of their indeterminate biliary stricture. GESA noted that POCPS is performed for the removal of difficult biliary stones as it allows for direct visualization of biliary stones and accurate targeting of the stone with EHL to fracture them to facilitate their removal.

The health professional considered that POCPS would result in prompt and efficient treatment of difficult stones and reduced numbers of ERCP procedures with associated cost saving.

The letter of support from Pancare, received with the application, highlighted that:

- POCPS is a more effective approach for clearing difficult biliary stones compared to repeated ERCP. POCPS is recommended in clinical guidelines.
- Early identification and removal of stones may enhance awareness, prevention, or early detection of biliary cancer.
- There is currently inequity to accessing this treatment due to a lack of public funding. However, ESC noted that the procedure is currently provided in some public hospitals.

### **Investigative application**

GESA was strongly supportive of the application and considered that POCPS is superior to standard ERCP-based techniques for the diagnosis of indeterminate biliary strictures. GESA proposed that MBS funding of POCPS may lead to earlier diagnosis and patient treatment, and reduce the number of ERCP and other procedures, to make a diagnosis. GESA also considered that patients would be generally reassured that a diagnosis has been made.

The health professional also supported the application and considered the benefits of POCPS would be in the accurate determination of the pathology of biliary structures, and result in inappropriate treatment of biliary strictures, such as surgery.

In their letter of support, Pancare highlighted the importance of early diagnosis of malignancy for treatment outcomes and quality of life. Pancare also highlighted the importance of avoiding multiple procedures, delays in diagnosis and the possibility of unnecessary surgical resection of benign strictures.

## **10. Characteristics of the evidence base**

### **Therapeutic application**

Two key trials were identified for the therapeutic application, one for each comparator. Their key features are summarised in Table 7.

**Table 7 Key features of the included evidence**

References	N	Design/duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
<b>POCPS-LL/EHL vs ERCP-ML</b>						
Angsuwatcharakon et al. (2019)	32	RCT 6 months	High <sup>a</sup>	Patients with very large CBD stones or with stones floating above a tapering CBD, and in whom extraction after standard sphincterotomy and/or EPLBD had failed	Complete stone clearance Single session stone clearance Overall adverse events	Yes
<b>POCPS-LL/EHL vs laparoscopic choledochotomy</b>						
Li et al. (2021)	157	R 12 months	Low	Patients with CBD stone diameter ≥2 cm as diagnosed by ultrasonography, CT and MRI	Complete stone clearance Single session stone clearance Overall adverse events	Yes

CBD=common bile duct; CT=computed tomography; EPLBD=endoscopic papillary large-balloon dilation; MRI=magnetic resonance imaging; RCT=randomised controlled trial.

<sup>a</sup> Due to high risk of incomplete results and selective report. Unclear allocation concealment and blinding.

The ADAR presented further supportive evidence was provided in form of naïve indirect comparisons. Of 28 studies, only six reported that all participants had prior ERCP. The commentary questioned the inclusion of studies with either no information on previous ERCP or with only a proportion of patients with prior ERCP. The commentary considered that none of the included single-arm studies were conducted in Australia or appeared particularly relevant to the Australian context.

Given the methodological deficiencies of the indirect comparison approach in the ADAR (overly restrictive and inconsistent search strategy, few details on the risk of bias assessment, double counting of evidence, multiple extraction errors, no description of methods for the pooling of results for indirect comparisons, no method for the indirect comparison except for a naïve comparison), the Commentary based its conclusions on the comparative evidence only. The pre-ESC response clarified that the meta-analysis was performed by calculating pooled proportions using RStudio.

The commentary noted that none of the identified studies (comparative or single-arm) were conducted in Australia or appeared particularly relevant to the Australian context. However, the inputs to modelling from studies conducted overseas were considered appropriate by the 2021 Advisory Board.

### Investigative application

Two key trials were identified for the investigative application, one randomised and one non-randomised. Their key features are summarised in Table 8.

**Table 8 Key features of the included evidence**

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base	Use in modelled evaluation
Accuracy and performance of the test (cross-sectional accuracy)	1 RCT, 1 cohort study	☒ k=2 n=86	1 RCT at risk of bias, concerns about applicability 1 cohort study at risk of bias, concerns about applicability	Yes*
Safety (overall adverse events)	1 RCT	☒ k=1 n=60	1 RCT at risk of bias, concerns about applicability	Yes
Change in patient management	3 cohort studies 1 CEA	☒ k=4 n=577	NR	No
Procedural success	1 RCT, 1 cohort study	☒ k=2 n=86	1 RCT at risk of bias, concerns about applicability 1 cohort study at risk of bias, concerns about applicability	Yes

CEA=cost-effectiveness analysis; k=number of studies; n=number of patients; NR=not reported; RCT=randomised controlled trial.

\*Draganov et al. (2012) was used as an alternative clinical input in the sensitivity analysis for the investigative application

Further supportive evidence was provided in form of naïve indirect comparisons. Given the methodological deficiencies of the indirect comparison previously stated, the commentary made its conclusions on the accuracy, safety, and procedural success based on the comparative evidence only.

None of the identified studies (comparative or single-arm) were conducted in Australia or appeared particularly relevant to the Australian context. However, the inputs to modelling from studies conducted overseas were considered appropriate by the 2021 Advisory Board.

## 11. Comparative safety

### Therapeutic application

Overall safety of POCPS-LL versus ERCP with mechanical lithotripsy or laparoscopic choledochotomy is summarised in Table 9 .

**Table 9 Summary of findings – comparison of POCPS-LL with ERCP-guided mechanical lithotripsy and laparoscopic choledochotomy in patients with difficult or infeasible biliary stones that have failed at least one attempt at removal via conventional extraction techniques**

Comparison	Number of studies (k), study design, patients (n)	Intervention absolute effect	Comparator absolute effect	Absolute difference (RD) [95% CI]	Relative effect (RR) [95% CI]	Quality of evidence (GRADE) <sup>a</sup>
POCPS-LL vs ERCP-ML	k=1, RCT, n=32 Angsuwatcharakon et al. (2019)	1/16 (6.3%)	2/16 (12.5%)	-0.06 (-0.26, 0.14)	0.50 (0.05-4.98)	⊕⊖⊖⊖ <sup>b</sup>
POCPS-LL vs laparoscopic choledochotomy	k=1, RCT, n=157 Li et al. (2021)	4/78 (5.1%)	9/79 (10.1%)	-0.06 (-0.15, 0.02)	0.45 (0.14-1.40)	⊕⊕⊖⊖ <sup>c</sup>

Note: RD and RR calculated post hoc using RevMan

Abbreviations: CI=confidence interval; ERCP-ML=endoscopic retrograde cholangiopancreatography-guided mechanical lithotripsy; N=number of participants; POCPS-EHL/LL=single operator, single use, peroral cholangiopancreatography-guided electrohydraulic lithotripsy/laser lithotripsy; RCT=randomised controlled trial; RD=risk difference; RR=relative risk

Source: Table 37 of the ADAR. GRADE assessment, edits and corrections to the original table were performed for the commentary

<sup>a</sup> GRADE Working Group grades of evidence (Guyatt et al., 2013)

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊖ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊖⊖ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊖⊖⊖ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

<sup>b</sup> Downgraded by 3 points due to concerns about the methodological quality of the study, imprecision and search strategy comprehensiveness

<sup>c</sup> Downgraded by 2 points due to concerns about imprecision and search strategy comprehensiveness

No statistically significant differences were found in the safety of POCPS-LL versus ERCP-guided mechanical lithotripsy or versus laparoscopic choledochotomy. The commentary evidence was of very low quality for the ERCP-guided mechanical lithotripsy comparison and of low quality for the laparoscopic choledochotomy comparison.

Angsuwatcharakon et al. (2019) reported one patient from each group developed mild post-ERCP pancreatitis, and one patient in the ERCP with mechanical lithotripsy developed mild post-sphincterotomy bleed.

Li et al. (2021) reported that in the POCPS-guided LL group, one patient (1.3%) experienced haemorrhage, one patient (1.3%) had residual stones, and two patients (2.6%) developed post-ERCP pancreatitis. In the laparoscopic choledochotomy group, there were two cases (2.6%) of haemorrhage, two cases (2.6%) of residual stones, two cases (2.6%) of bile leakage, one case (1.3%) of abdominal infection, and one case (1.3%) of common bile duct stricture. Comparative evidence was presented for POCPS-guided LL only. Comparative studies on POCPS-guided EHL were not identified. The commentary considered that it was unclear whether the same clinical claim holds for POCPS-guided EHL.

Further supportive evidence was provided in form of naïve indirect comparisons. Additional safety data for cholangitis, bleeding, and peritonitis from single-arm studies was provided in an appendix, but no interpretation was provided. Proper assessment of the certainty of evidence, such as GRADE assessment, was not provided in the ADAR. Given the methodological deficiencies of the indirect comparison approach in this ADAR (overly restrictive and inconsistent search strategy, few details on the risk of bias assessment, double counting of evidence, multiple

extraction errors, no description of methods for the pooling of results for indirect comparisons, no method for the indirect comparison except for a naïve comparison), a GRADE assessment was not performed for the commentary.

## Investigative application

Overall safety of POCPS-guided biopsy versus ERCP-guided brush cytology alone is summarised in Table 10.

**Table 10 Summary of findings – comparison of safety outcomes (overall adverse events) with POCPS and ERCP-guided brush cytology or intraductal biopsy in patients with indeterminate biliary strictures**

Comparison	Number of studies (k), study design; patients (n)	Intervention absolute effect	Comparator absolute effect	Absolute difference	Quality of evidence (GRADE) <sup>a</sup>
POCPS biopsy vs ERCP brush cytology	k=1, 1 RCT, n=60 Gerges et al. (2020)	2/31 (6.5%)	3/29 (10.3%)	-3.8% (p=0.59)	⊕⊖⊖⊖ <sup>b</sup>

Source: Table 60 of the ADAR. GRADE assessment, edits and corrections to the original table were performed for the commentary. Abbreviations: ERCP-BC= endoscopic retrograde cholangiopancreatography-guided brush cytology; MRCP= magnetic resonance cholangiopancreatography; N = number of participants; NR = not reported; POCPS-B= single operator, single use, peroral cholangiopancreatography-guided biopsy; RoB= Risk of Bias.

<sup>a</sup> GRADE Working Group grades of evidence (Guyatt et al., 2013)

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊖ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊖⊖ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊖⊖⊖ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

<sup>b</sup> Downgraded due to concerns about indirectness, imprecision, and search strategy comprehensiveness. One RCT with serious applicability concerns reported non-significantly lower overall adverse events rate for POCPS compared with ERCP-BC ERCP-BC=endoscopic retrograde cholangiopancreatography-guided brush cytology; POCPS=peroral cholangiopancreatography; RCT=randomised controlled trial; RR=risk ratio

No statistically significant differences were found in the overall safety of POCPS vs ERCP-guided brush cytology. The commentary considered the evidence was of very low quality.

Gerges et al. (2020) reported that two patients (6.5%) in the POCPS group experienced pancreatitis. In the ERCP-guided brush cytology group, there was one case each of cholangitis, cholecystitis, and bleeding. All adverse events were considered mild and were treated conservatively. The commentary considered there are uncertainties around the applicability of the evidence, as patients were not required to have a prior failed ERCP attempt to obtain a sample.

No direct evidence was identified for the comparison of POCPS-guided biopsy versus ERCP-guided intraductal biopsy.

The ADAR presented further supportive evidence was provided in form of naïve indirect comparisons. Additional safety data for cholangitis, cholecystitis, pancreatitis, bleeding, perforation, abdominal pain and cardiovascular adverse events from single-arm studies was provided in an appendix, but no interpretation was provided.

Consequent harms of testing (i.e., those mediated through subsequent changes to clinical management) were not presented in the ADAR.

The pre-MSAC response provided additional detailed adverse safety data from the non-comparative studies.

**Table 11 Comparative safety for ERCP, therapeutic POCPS and investigative POCPS**

Adverse events	ERCP <sup>a</sup>	Therapeutic POCPS	Investigative POCPS
Pancreatitis	3.5%–9.7%	NR	0%–11.6% (8 studies)
Cholangitis	0.5%–3.0%	0.64%–11.9% (8 studies)	0–12.7% (10 studies)
Cholecystitis	0.5%–5.2%	NR	0% (3 studies)
Bleeding	0.3%–9.6%	0%–2.9% (4 studies)	0–3.2% (7 studies)
Perforation	0.08%–0.6%	NR	0.4% (1 study)
Sedation-related AE's	24.6%	NR	NR

Source: Pre-MSAC response

ERCP =endoscopic retrograde cholangiopancreatography; POCPS=peroral cholangiopancreatotomy

<sup>a</sup> Sourced from ESGE Guideline (Dumonceau et al., 2020)

<sup>b</sup> Sourced from all identified indirect non-comparative studies presented in the ADAR (Appendix C supplementary data)

## 12. Comparative effectiveness

### Therapeutic application

Results of the primary effectiveness outcome, complete stone clearance, are summarised in Table 12.

**Table 12 Complete stone clearance with POCPS-LL**

Comparison	Number of studies (k), study design; patients (n)	Intervention absolute effect	Comparator absolute effect	Absolute difference (RD) [95% CI]	Relative effect (RR) [95% CI]	Quality of evidence (GRADE) <sup>a</sup>
POCPS-LL vs ERCP-ML	k=1 RCT n=32	16/16 (100%)	10/16 (62.5%)	0.38 (0.13, 0.62)	1.57 (1.07-2.30)	⊕⊕⊕⊖ <sup>b</sup>
POCPS-LL vs laparoscopic choledochotomy	k=1 RCT n=157	72/78 (92.3%)	76/79 (96.2%)	-0.04 (-0.11, 0.03)	0.96 (0.89-1.04)	⊕⊕⊕⊕ <sup>c</sup>

<sup>a</sup> GRADE Working Group grades of evidence (Guyatt et al., 2013)

<sup>b</sup> Downgraded by 2 points due to concerns about the methodological quality of the study and search strategy comprehensiveness. The pre-ESC response considered it should be rated as 'Moderate quality'.

<sup>c</sup> Downgraded by 1 point due to concerns about the search strategy comprehensiveness. The pre-ESC response considered it should be rated "High quality".

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊖ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊖⊖ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊖⊖⊖ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CI = confidence interval; ERCP-ML= endoscopic retrograde cholangiopancreatography-guided mechanical lithotripsy; N = number of participants; POCPS-EHL/LL= single operator, single use, peroral cholangiopancreatotomy-guided electrohydraulic lithotripsy/laser lithotripsy; RD = risk difference; RoB = Risk of Bias; RR = relative risk

Source: Table 33 of the ADAR.

Comparative evidence was presented for POCPS-guided laser lithotripsy only. Comparative studies on POCPS-guided electrohydraulic lithotripsy were not identified. The commentary

considered that it was unclear whether the same clinical claim holds for POCPS-guided electrohydraulic lithotripsy.

Secondary outcome of single session stone clearance was consistent with the primary outcome. No other outcomes were presented in the ADAR.

The commentary considered that POCPS-guided laser lithotripsy in patients with difficult or infeasible biliary stones that have failed at least one attempt at removal via conventional extraction techniques appears to be superior to ERCP-guided mechanical lithotripsy and non-inferior to laparoscopic choledochotomy.

The ADAR presented further supportive evidence based on meta-analysis of single arm studies that assessed either POCPS or ERCP. The commentary highlighted the methodological deficiencies with the naïve indirect comparison approach outlined in Characteristics of the evidence base.

**Table 13 Complete stone clearance with POCPS (indirect evidence)**

Comparison	Number of studies (k), study design; patients (n)	Intervention absolute effect [95% CI]	Comparator absolute effect [95% CI]
POCPS Legacy system	k=16, Single arm cohort <sup>a</sup> n=628	89.7% <sup>c</sup> (82.9%-95.2%) I <sup>2</sup> =79%	-
POCPS Digital system	k=12, Single arm cohort <sup>a,b</sup> n=798	95.5% (91.5%-98.4%) I <sup>2</sup> = 64%	-
ERCP	k=2, Single arm cohort <sup>a</sup> n=136	-	53.3% (28.2%, 77.6%) I <sup>2</sup> = 88%

Source: Tabled 34-36, Figure 9 of the ADAR; Table 5-6 of the pre-ESC response.

<sup>a</sup> Not all studies were single arm studies.

<sup>b</sup> Includes Angsuwatcharakon et al. (2019) and Li et al. (2021) which accounted for 5.6% and 11.3% of meta-analysis

<sup>c</sup> Updated from 94.1% [71.3%-99.9%] presented in Table 35 1673 ADAR

The commentary noted the meta-analysis for digital POCPS-EHL/LL should not have included the randomised studies. The ADAR considered the majority of patients in the POCPS meta-analysis were from the USA and the results can be reasonably generalised to Australia with respect to the treatment of difficult biliary stones and ethnic background. The ADAR considered the heterogeneity may be due to differences in patient baseline characteristics, study location, varied definition of difficult biliary stones, varied location of stones, previous attempted treatments as well as inter-operator procedural capability and familiarity. The ADAR noted limitations of the ERCP studies including potential differences due to the clinical setting and age of the study.

## Investigative application

The direct evidence for diagnostic accuracy of POCPS-guided biopsy compared to ERCP-guided brush cytology and intraductal biopsy are presented in Table 14.

The ADAR did not identify any studies on the diagnostic accuracy of combined POCPS-guided biopsy and visualisation. However, the ADAR considered that POCPS-guided visualisation is an essential component of the diagnostic and standard clinical practice in Australia utilises both POCPS-guided visualisation and POCPS-guided biopsy to inform the diagnosis of an indeterminate biliary stricture.

**Table 14 Results of test accuracy across studies evaluating POCPS-B compared with ERCP-BC: direct comparative evidence**

Study ID, Country Generation	Study Design, RoB, Quality of evidence (GRADE) <sup>a</sup>	Prior Test	Reference Standard	Test Accuracy Outcomes	POCPS-B	ERCP-BC	Difference (p-value)
Gerges et al. (2020), multiple Digital	RCT Low risk of bias Concerns about applicability ⊕⊕⊕⊕ <sup>b</sup>	MRCP	Clinical follow up (6 months) or histological examination	Sensitivity	68.2%	21.4%	46.8% (<0.01)
				Specificity	62.5%	85%	-22% (0.25)
				PPV	100%	100%	0%
				NPV	45.5%	64.7%	-19.2%
Draganov et al. (2012), USA Legacy	NRCT At risk of bias Concern about applicability ⊕⊕⊕⊕ <sup>b</sup>	ERCP (92%)	Clinical follow up (median 21.8 months) or histological examination	Sensitivity	77%	5.8%	70.7% (p<0.0001)
				Specificity	100%	100%	0%
				PPV	100%	100%	0%
				NPV	69.2%	36%	33.2%

Abbreviations: ERCP-BC= endoscopic retrograde cholangiopancreatography-guided brush cytology; MRCP = magnetic resonance cholangiopancreatography; N = number of participants; NR = not reported, NRCT = non-randomised controlled trial; POCPS-B = single operator, single use, peroral cholangiopancreatography-guided biopsy; RoB = risk of bias.

Source: Table 57 of the ADAR. GRADE Assessment, edits and corrections to the original table were conducted for the commentary.

<sup>a</sup> GRADE Working Group grades of evidence (Guyatt et al., 2013)

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊕ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊕⊕ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊕⊕⊕ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

<sup>b</sup> Downgraded due to concerns about the methodological quality of the studies, indirectness, imprecision, and search strategy comprehensiveness. The pre-ESC response considered the rating should be 'Low quality'.

**Table 15 Results of test accuracy across studies evaluating test accuracy of POCPS-B compared with ERCP-IB: direct comparative evidence**

Study ID, Country Generation	Study Design, RoB, Quality of evidence (GRADE) <sup>a</sup>	Prior Test	Reference Standard	Test Accuracy Outcomes	POCPS-B	ERCP-IB	Difference (p-value)
Draganov et al. (2012), USA Legacy	NRCT At risk of bias Concern about applicability ⊕⊕⊕⊕ <sup>b</sup>	ERCP (92%)	Clinical follow up (median 21.8 months) or histological examination	Sensitivity	77%	29.4%	47.1% (p=0.0215)
				Specificity	100%	100%	0%
				PPV	100%	100%	0%
				NPV	69.2%	42.8%	26.4%

Abbreviations: ERCP-IB = endoscopic retrograde cholangiopancreatography-guided intraductal biopsy; MRCP= magnetic resonance cholangiopancreatography; N = number of participants, NR = not reported, POCPS-B= single operator, single use, peroral cholangiopancreatography-guided biopsy, RoB= risk of bias.

Source: Table 58 of the ADAR. Edits and corrections to the original table are marked in italics.

<sup>a</sup> GRADE Working Group grades of evidence (Guyatt et al., 2013)

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊕ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊕⊕ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊕⊕⊕ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

<sup>b</sup> Downgraded due to concerns about the methodological quality of the studies, indirectness, imprecision, and search strategy comprehensiveness

The direct evidence for procedural success of POCPS-guided biopsy compared to ERCP-guided brush cytology and intraductal biopsy are presented in Table 16 and Table 17.

**Table 16 Proportion of indeterminate results across studies evaluating POCPS-B compared with ERCP-BC**

Study ID, Country Generation	Study Design, RoB Quality of evidence (GRADE) <sup>a</sup>	Prior Test	POCPS-B N/N %	ERCP-BC N/N %	Difference
Gerges et al. (2020), multiple continents Digital	RCT High risk of bias <sup>b</sup> Concerns about applicability ⊕⊕⊕⊕ <sup>c</sup>	MRCP	4/30 (13.3%)	7/27 (25.9%)	12.6%
Draganov et al. (2012), USA Legacy	NRCT High risk of bias <sup>d</sup> Concerns about applicability ⊕⊕⊕⊕ <sup>c</sup>	ERCP	2/25 (8.0%)	4/25 (16.0%)	8.0%

Abbreviations: ERCP-BC= endoscopic retrograde cholangiopancreatography-guided brush cytology; MRCP = magnetic resonance cholangiopancreatography; N = number of participants; POCPS-B= single operator, single use, peroral cholangiopancreatography-guided biopsy; RCT = randomised controlled trial; RoB = risk of bias.

Source: Table 70 of the ADAR. Edits and corrections to the original table are marked in italics.

<sup>a</sup> GRADE Working Group grades of evidence (Guyatt et al., 2013)

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊕ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊕⊕ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊕⊕⊕ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

<sup>b</sup> High risk of bias due to potential unequal randomisation (different prevalence of malignancy), potential difference application of the reference standard, no prior ERCP.

<sup>c</sup> Downgraded due to concerns about the methodological quality of the studies, indirectness, imprecision, and search strategy comprehensiveness. The Pre-ESC response assessed the quality of evidence as being 'Low quality'.

<sup>d</sup> High risk of bias due to lack of randomisation, reference standard (surgery) used variably and lack of blinding.

**Table 17 Proportion of indeterminate results across studies evaluating POCPS-B compared with ERCP-IB**

Study, Country Generation	Study Design, RoB Quality of evidence (GRADE) <sup>a</sup>	Prior Test	POCPS-B N/N %	ERCP-IB N/N %	Difference
Draganov et al. (2012), USA Legacy	NRCT High risk of bias Concerns about applicability ⊕⊕⊕⊕ <sup>b</sup>	ERCP	2/25 (8.0%)	7/26 (26.9%)	18.9%

Abbreviations: ERCP-IB= endoscopic retrograde cholangiopancreatography-guided intraductal biopsy; MRCP = magnetic resonance cholangiopancreatography; N = number of participants; POCPS-B= single operator, single use, peroral cholangiopancreatography-guided biopsy; RCT = randomised controlled trial; RoB = risk of bias.

Source: Table 71 of the ADAR. Edits and corrections to the original table are marked in italics.

<sup>a</sup> GRADE Working Group grades of evidence (Guyatt et al., 2013)

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊕ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

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⊕⊕⊕⊕ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

<sup>b</sup> Downgraded due to concerns about the methodological quality of the studies, indirectness, imprecision, and search strategy comprehensiveness. The Pre-ESC response assessed the quality of evidence as being 'Low quality'.

One RCT with small sample size reporting procedural success was identified (Gerges et al., 2020); this study had serious applicability concerns (patients had no previous unsuccessful ERCP attempt) and was not powered for the outcome. ESC highlighted that Gerges et al (2020) may not have been effectively randomised as the two arms had a different prevalence of

malignancy and the reference standard was not consistent. Gerges et al (2020) reported a similar number of procedures to get a final diagnosis for both arms.

They reported lower rates of indeterminate results for POCPS compared with ERCP-BC, but its statistical or clinical significance is unclear.

The commentary considered data from Draganov et al. (2012) are likely more applicable to this ADAR, however, that study also had a small sample size, was at risk of bias (no blinding of pathologists to the clinical history), and was not powered for this outcome. They also reported lower rates of indeterminate results for POCPS compared with ERCP-BC and ERCP-IB, however, its statistical or clinical significance is unclear.

Further supportive evidence was provided in form of single-arm studies for the intervention, but no evidence was identified for the comparator. No indirect comparison was therefore possible.

The identified evidence for change in management of POCPS-guided biopsy compared to ERCP-guided brush cytology and intraductal biopsy are presented in Table 18.

**Table 18 Results of change in management across studies evaluating POCPS-V and POCPS-B**

Study ID, Country Study Design Generation	N	Prior Test	Change in management N/N %	Avoided Surgery N/N %	Reduction In Repeated Procedures
Almadi et al. (2020), Prospective, multicentre Digital	n=289	ERCP (60.2%)	249/289 (86.2%; 95% CI 81.6- 89.9%)	22.2%	NR
Chen et al. (2011) Prospective, multicentre Legacy	Diagnostic POCPS: n=226	ERCP (86.2%)	64%; 95% CI 57- 70%	25%	NR
Prat et al. (2019) Prospective, multicentre Legacy	Indeterminate biliary strictures: n=48	Inconclusive ERCP-BC ±CT/MRI Not amenable to EUS-FNA	28/48 (58.3%) Adequate management before POCPS: 21/48 (56.2%) Adequate management after POCPS: 41/48 (85.4%), p<0.001	26/48 (54.2%)	NR
Deprez et al. (2018) Cost-effectiveness study NR	NR	ERCP	NR	NR	Diagnostic procedures: - 22% Surgical procedures: - 91% Total procedures: -31%

Abbreviations: CI=confidence interval; ERCP = endoscopic retrograde cholangiopancreatography; EUS-FNA= endoscopic ultrasound; N = number of participants; NR = not reported; POCPS-V/B= single operator, single use, peroral cholangiopancreatography-guided visualisation/biopsy

single operator, single use, peroral cholangiopancreatography-guided visualisation/biopsy

Source: Table 77 of the ADAR. Edits and corrections to the original table are marked in italics.

No comparative evidence for the change of management was identified. The commentary considered that there is a large amount of uncertainty in the interpretation of the presented evidence and its applicability to the Australian context. In particular, Australian practice might be different in terms of next steps depending on the clinician's judgement of the likelihood of a malignant cause, and to the population of interest to this ADAR (i.e., patients with a prior failed ERCP attempt at biopsy/cytology).

The ADAR makes a claim that linked health outcomes identified in the submission are the following:

- Avoided repeated procedures
- Avoided delays in treatment
- Avoided unnecessary surgical resection.

However, no evidence is presented in Section 2B.7 to directly support this claim.

The commentary considered the linked evidence approach in the ADAR does not integrate the individual steps into a coherent argument to support its clinical claim for the investigative application. The pre-ESC response claimed POCPS-guided visualisation and biopsy results in superior effectiveness compared with ERCP-guided brush cytology and/or intraductal biopsy and providing superior accuracy and a reduced number of inconclusive test results. The pre-ESC response considered that this would result in a significant change in the management of patients including a reduction in repeated diagnostic procedures and unnecessary surgical resection of benign strictures. These outcomes have numerous health impacts on patients including a reduction in a range of adverse events and delays in diagnosing malignancy which can place patient at greater risk of a worse clinical outcome.

### **Clinical claim**

### **Therapeutic application**

The ADAR claimed that POCPS-guided LL/EHL results in superior effectiveness compared with ERCP-guided mechanical lithotripsy and laparoscopic choledochotomy.

The commentary considered the clinical effectiveness claim for Comparator 2 (laparoscopic choledochotomy) is not supported by the evidence. The pivotal study by Li et al. (2021), presented as the only evidence for Comparator 2, was a non-inferiority study. Therefore, only a non-inferiority claim can be made.

The ADAR claimed POCPS-guided LL/EHL results in non-inferior safety compared with ERCP-guided mechanical lithotripsy and superior safety compared with laparoscopic choledochotomy. The commentary considered the claim of superior safety compared with laparoscopic choledochotomy was not supported by the evidence. There were no statistically significant differences in the safety of POCPS-LL versus laparoscopic choledochotomy and the evidence was of very low quality. The commentary considered the claim should be revised to non-inferior safety.

The pre-ESC response accepted the claim of non-inferiority compared with laparoscopic choledochotomy but highlighted that there may be other benefits such as shorter length of hospitalisation and quality of life. The pre-ESC response claimed patients would typically undergo a repeat endoscopic extraction attempt three times before they are referred to surgery as it is kept as a last resource, only attempted when no other non-invasive procedures are possible.

The commentary considered that it was unclear whether the same clinical claim holds for POCPS-guided EHL as no comparative evidence for POCPS-guided EHL was identified.

### **Investigative application**

The use of POCPS-guided visualisation and biopsy results in superior effectiveness compared with ERCP-guided brush cytology and/or intraductal biopsy.

The use of POCPS-guided visualisation and biopsy results in non-inferior safety compared with ERCP-guided brush cytology and/or intraductal biopsy.

The commentary considered the claim for superior effectiveness may need to be revised from superior to non-inferior, given concerns about the consistency, applicability, and overall certainty of the very low-quality evidence identified.

The commentary considered that the clinical claim of non-inferior safety is likely appropriate.

## **13. Economic evaluation**

### **Overview and rationale of the economic evaluation**

#### ***Therapeutic application***

This ADAR presented a CEA to assess the value of POCPS-guided EHL/LL compared to ERCP-guided mechanical lithotripsy and laparoscopic choledochotomy, and the downstream healthcare resource utilisation impact associated with difficult biliary stones. The reason why a CEA was preferred to a CUA for this submission is due to the complexity of the downstream healthcare resources utilisation associated with the treatment of difficult biliary stones, and the limited availability of associated utility data, which would make the results of the assessment highly uncertain.

The economic model was based on the clinical claim of superiority and under that clinical claim a cost effectiveness is appropriate, however as the clinical claim for laparoscopic choledochotomy has been revised to non-inferior safety, the commentary considered a cost minimisation analysis may also be appropriate for this comparator.

This economic evaluation presents the incremental cost per successful stone removal. As recommended by PASC, the cost to the MBS and hospital budgets (consumables and capital) have both been included. A summary of the key characteristics of the economic evaluation of therapeutic POCPS is detailed in Table 19.

**Table 19: Summary of the therapeutic economic evaluation**

Component	Description
Perspective	Australian Government
Population	Difficult biliary stones
Intervention	POCPS-EHL/LL
Comparator	ERCP-ML, laparoscopic choledochotomy
Type of economic evaluation	Cost effectiveness analysis (CEA)
Sources of evidence	2021 Advisory Board, Li et al. (2021), Angsuwatcharakon et al. (2019)
Outcomes	Incremental cost per successful stone removal
Methods used to generate results	Decision analytic tree
Software packages used	Microsoft Excel 2021®

Abbreviations: ERCP-ML = endoscopic retrograde cholangiopancreatography-guided mechanical lithotripsy; POCPS-guided EHL/LL = single operator, single use, peroral cholangiopancreatography-guided electrohydraulic lithotripsy/ laser lithotripsy

To determine the cost effectiveness of POCPS-guided EHL/LL in patients with difficult biliary stones, an incremental cost per successful stone removal was calculated using the data from the two pivotal RCTs presented in the clinical evaluation (Angsuwatcharakon et al., 2019; Liu et al., 2017). Lowering the number of repeated endoscopic extraction attempts avoids several poor patient outcomes, including increased healthcare resource utilisation, increased medical costs, safety implications and delays in treatment (Boix & Lorenzo-Zúñiga, 2011; Chandrasekhara et al., 2017; Li et al., 2021). Additionally, POCPS-guided LL/EHL lowers the number of patients referred to surgical extraction (laparoscopic choledochotomy) which is a more invasive procedure associated with significantly longer hospital stays (Li et al., 2021).

Limitations of the studies mentioned in the clinical evaluation include a small number of participants in (Angsuwatcharakon et al., 2019), and different study locations for both RCTs, where the clinical setting, costs and practices may not fully reflect the Australian context. The commentary considered that it is also unclear whether the 2021 Advisory Board has attempted to mitigate this uncertainty by validating these outcomes for the Australian setting. The Clinical Advisory Board Minutes Summary supports the use of data from Li et al. (2021) in the base case analysis due to the large number of participants and closely aligned estimates to those presented by physicians.

The model structure used to assess the cost effectiveness of POCPS for therapeutic application is consistent with the feedback provided during the 2021 Advisory Board, international clinical guidelines (Williams et al., 2017) and several published economic analysis. A similar CEA structure was used in the recent POCPS evidence appraisal report by Health Technology Wales (Health Technology Wales, 2020).

The international clinical guidelines state that ERCP (supplemented by EPBD with prior sphincterotomy, mechanical lithotripsy or cholangioscopy) is a successful treatment for the removal of difficult ductal stones (Williams et al., 2017). The alternative in the model for ERCP is choledochotomy, which is also assumed in the guidelines as an appropriate surgical extraction method. Additionally, the guidelines note that the use of EHL or LL should be considered where options fail to achieve duct clearance, which is consistent with the intervention in the ADAR.

The commentary noted the model structure in the ADAR is similar to that developed by Health Technology Wales (HTW) in terms of the comparators for diagnostic and therapeutic applications of POCPS, model structure and outcomes. Key differences include the cost data and resource utilisation. Additionally, the HTW model considers POCPS in comparison to conventional therapy

as a first line treatment for the removal of difficult biliary stones, and POCPS intervention after unsuccessful ERC. While there may be greater certainty with a cost-effectiveness analysis, the commentary considered that a cost-utility model is more informative when comparing across health technology assessments, and therefore beneficial in the decision-making process. While the HTW model did not provide a cost-utility model for the therapeutic application, a cost-utility model was reported for the investigative application, and as such enough evidence may be available for a cost-utility model, at least for the investigative application.

### ***Investigative application***

The clinical evaluation demonstrates that relative to ERCP-guided brush cytology and/or intraductal biopsy, POCPS-guided visualisation and biopsy has superior effectiveness and non-inferior safety.

This submission presents a CEA to assess the value of POCPS-guided visualisation and biopsy compared to ERCP-guided brush cytology and/or intraductal biopsy, and the downstream healthcare resource utilisation associated with indeterminate biliary strictures given the complexity of the potential downstream impacts following the diagnosis. The reason why a CEA was preferred to a CUA for this submission is due to the complexity of the downstream healthcare resources utilisation associated with the diagnosis of indeterminate biliary strictures. PASC considered that sufficient data may not be available about the downstream consequences given the multiple potential diagnoses/outcomes, which would make the results of the assessment highly uncertain (1673 Ratified PICO, page 19).

The commentary considered that this approach is appropriate given the clinical claims and availability of healthcare resource utilisation data. The commentary noted that HTW reported a cost-utility for the investigative application, and as such enough evidence may be available for a cost-utility model (Health Technology Wales, 2020).

To determine the cost effectiveness of POCPS-guided visualisation and biopsy in patients with indeterminate biliary strictures, incremental cost per correctly diagnosed patient was calculated using the data from key trials presented in the clinical evaluation (Minami et al., 2021; Navaneethan et al., 2015b). Reducing the number of patients with benign strictures who are incorrectly referred to surgery avoids several poor patient outcomes, including prolonged hospital stays, increased medical costs and mortality. Additionally, due to the lower number of indeterminate results, POCPS-guided visualisation reduces the number of repeated ERCP procedures, improving patient safety and reducing costs (ASGE). These repeated procedures may also lead to a substantial delay in diagnosis, particularly considering patients with inconclusive results must wait at least three months between each ERCP procedure. Delays in diagnosing malignancy place patients at a high risk for disease progression, which significantly impacts long-term survival (Jang et al., 2005; Victor et al., 2012).

The commentary highlighted that the sensitivity and specificity for ERCP-BC or forceps biopsy were correctly reported in the model where the specificity was 100% and denoted in the model as 99% (Navaneethan et al., 2015a). A specificity of 100% suggests that the intervention detects no false positives which may be plausible considering the diagnostic process relies on visual identification. This is based on a meta-analysis and systematic review of six studies that reported the pooled sensitivity and specificity of intraductal biopsies and brushing for cytology for the diagnosis of malignant biliary strictures. A key limitation of the systematic review and meta-analysis is the inclusion of low-quality studies where specificity of ERCP-BC may be overestimated, although there is a low risk of bias in most of the included studies as indicated in the key evidence and outcomes section in the ADAR.

Patients who are incorrectly diagnosed undergo inappropriate treatment or face late-stage treatment with poor patient outcomes and is associated with significant cost. The cost of incorrect diagnosis for malignant patients are not included in the economic analysis as there is a high degree of uncertainty in the duration of delay to a correct diagnosis. In addition, cholangiocarcinoma is understood to show no obvious symptoms or signs (such as jaundice) until it reaches later stage (Patel et al., 2014). Similarly, the cost for true benign patients incorrectly diagnosed is also not included, as there is high variation in additional staging for diagnosis and the treatment modalities which are hard to assess. The Applicant considers this approach conservative as retesting alone in incorrectly diagnosed patients is a significant cost. The Applicant has prepared a clean CEA demonstrating the value of POCPS when compared to ERCP in more accurate diagnosis for indeterminate biliary strictures and avoidance of unnecessary surgeries for benign patients, which are PASC agreed outcomes.

This approach is aligned with the model presented in application 1072 [endoscopic ultrasound (EUS) and endoscopic ultrasound guided fine needle aspiration (EUS-FNA) for diagnosing and staging gastrointestinal neoplasms], which claimed superior diagnostic accuracy, reduction in unnecessary surgeries, and non-inferior safety in a comparable disease area. The submission presented decision analytic model using data from the literature to evaluate the performance characteristics of EUS and estimate the cost implications associated with reducing unnecessary surgical procedures. Performing EUS and consequently avoiding unnecessary surgical procedures resulted in a cost saving of between \$1,506.50- \$2,845.14 per patient for gastric cancer stage and \$2,149.95 per patient for pancreatic cancer staging and subsequently obtained a positive MSAC recommendation.

The model structure for application 1072 is aligned with the model structure presented in this ADAR, where similarities exist including model type (decision analytic model), cost data sourcing methods, downstream healthcare resourced utilisation and outcomes

A summary of the key characteristics of the economic evaluation of therapeutic POCPS is detailed in Table 20.

**Table 20 Summary of the investigative economic evaluation**

Component	Description
Perspective	Australian Government
Population	Indeterminate biliary strictures
Intervention	POCPS-V with POCP-B
Prior testing	ERCP-BC and/or ERCP-IB
Comparator	ERCP-guided brush cytology and/or ERCP-guided intraductal biopsy (repeated)
Type of economic evaluation	Cost effectiveness analysis (CEA)
Sources of evidence	2021 Advisory Board, Gerges et al. (2020), Minami et al. (2021)
Outcomes	Incremental cost per correctly diagnosed patient
Methods used to generate results	Decision analytic tree
Software packages used	Microsoft Excel 2021®

Abbreviations: ERCP-BC/IB = endoscopic retrograde cholangiopancreatography-guided brush cytology/intraductal biopsy; POCPS-V/B = single operator, single use, peroral cholangiopancreatography-guided visualisation/biopsy Type of economic evaluation

## **Type of economic evaluation**

### ***Therapeutic application***

This economic evaluation presents the incremental cost per successful stone removal. As recommended by PASC, the cost to the MBS and hospital budget (consumables and capital) have both been included.

The model structure depicts the current clinical management paradigm (either ERCP-guided mechanical lithotripsy or laparoscopic choledochotomy) and the proposed alternative (POCPS-guided EHL/LL) for removing difficult biliary stones. A hypothetical cohort of 1,000 patients is designated to receive either POCPS-guided EHL/LL or the comparator. A weighted comparator was calculated based on the proportion of ERCP-guided mechanical lithotripsy and laparoscopic choledochotomy use in Australian practice, with 67% of patients treated with ERCP-guided mechanical lithotripsy and 33% of patients treated with laparoscopic choledochotomy (2021 Advisory Board). In all scenarios, patients with successful stone clearance after the first extraction attempt exit the model (83% for POCPS, 63% for ERCP, 96% for laparoscopic choledochotomy). The remaining patients with unsuccessful stone clearance undergo a second stone removal attempt before being referred to surgery (laparoscopic choledochotomy) with the same success rate for each procedure type. The proportion of patients receiving a particular intervention at each step of the model is based on data from two pivotal RCTs (Angsuwatcharakon et al., 2019; Li et al., 2021) and the 2021 Advisory Board.

The model presented in the ADAR only includes two repeat procedures before receiving surgery. This is in line with the therapeutic procedure MBS item for POCPS in the Ratified PICO that states patients can receive a maximum of three procedures per year.

### ***Investigative application***

The model structure (Figure 3 and Figure 4) depicts the current clinical management paradigm (ERCP-guided brush cytology and/or intraductal biopsy) and proposed alternative (POCPS-guided visualisation and biopsy) for the diagnosis of indeterminate biliary strictures. A hypothetical cohort of 1,000 patients is designated to receive either POCPS-guided EHL/LL or the comparator. In both scenarios, patients achieving a diagnosis are subsequently treated and exit the model. Based on physician advice, patients with indeterminate results were assumed to either undergo surgical resection, due to concerns of malignancy, or were re-evaluated with a repeat diagnostic procedure (i.e. ERCP-guided brush cytology and/or intraductal biopsy in the comparator arm and POCPS-guided biopsy and visualisation in the intervention arm). Those remaining undiagnosed after the repeat procedure were assumed to undergo surgical resection (validated by the 2021 Advisory Board).

This model structure is in line with feedback from the 2021 Advisory Board and international consensus guidelines for the diagnosis of indeterminate biliary strictures (Angsuwatcharakon et al., 2021).

The commentary considered that the structure of the model is appropriate and considers the primary outcome of cost per correctly diagnosed patient. The applicant acknowledged the importance of capturing all listed safety outcomes, however these are not captured in the available clinical evidence base. Given the non-inferior safety profile, it is assumed that safety profiles do not greatly differ between the intervention and the comparator.

This ADAR has included a one-off cost for the incorrect diagnosis of malignant biliary structures (incorrectly diagnosed as benign) to account for this factor. It is noted that the number of patients with malignant disease diagnosed as benign is more frequent in the comparator arm, amounting to 18 and 228 for POCPS and ERCP respectively. The cost of this impact is calculated using a terminal care cost which amounts to \$30,001 AUD (2009/2010) and reflects the yearly average health care costs of patients who died from cancer (\$37,912 when inflated to 2021 costs). The commentary considered that this cost may be appropriate as it is reflective of the Australian health care setting and acts as an opportunity cost for receiving a correct malignant diagnosis, assuming patients with incorrect diagnosis die from cancer. The method is appropriate given the best available data provided in other clinical studies and economic models. However, this assumption should be tested in a sensitivity analysis to assess the impact of sensitivity and specificity with the inclusion of inconclusive test results. This is not considered in the sensitivity model in this ADAR.

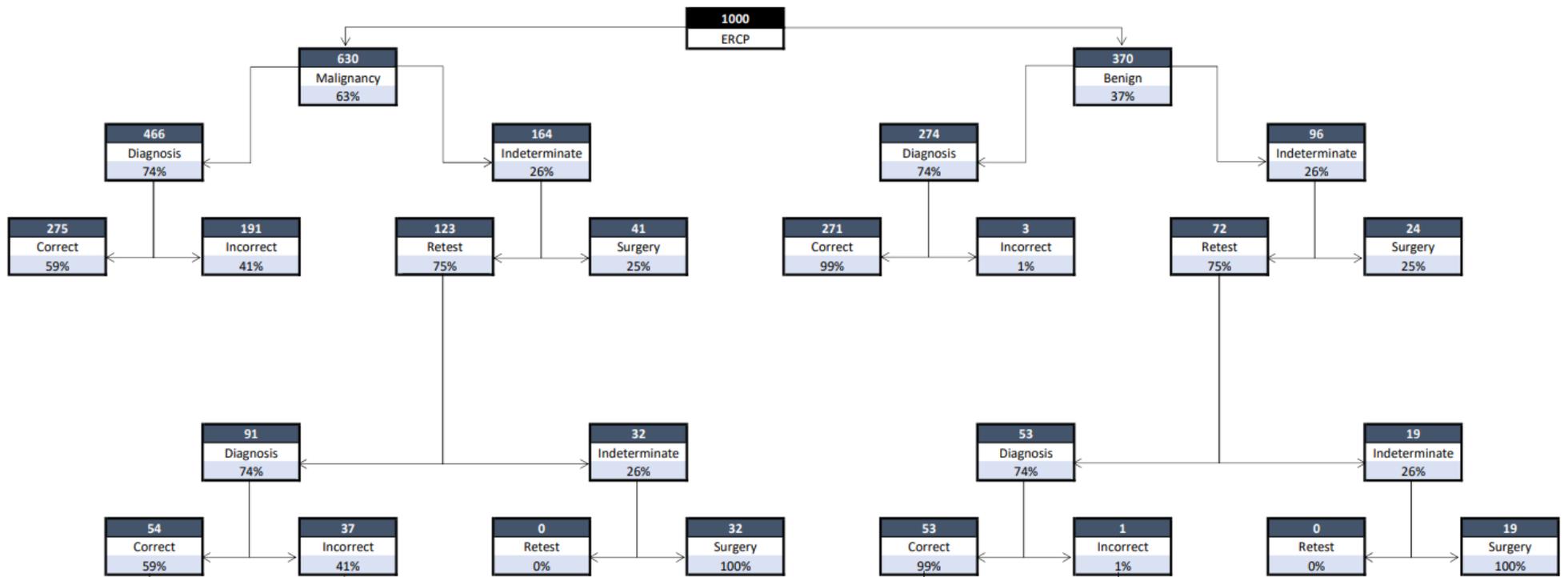


Figure 3 Structure of analytic tree for indeterminate biliary strictures (comparator arm)

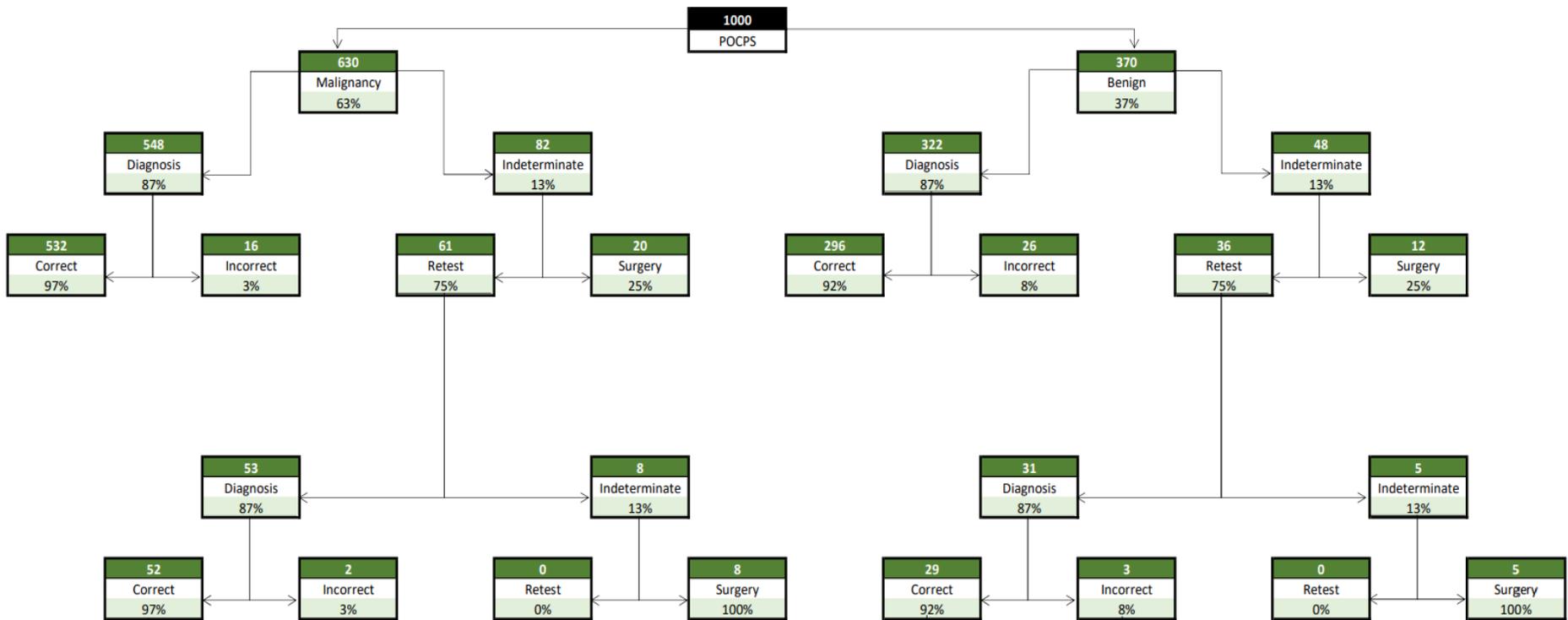


Figure 4 Structure of analytic tree for indeterminate biliary strictures (intervention arm)

## Generation of the base case

### *Therapeutic application*

Single session stone clearance was used as the key clinical input for this analysis. The two identified RCTs presented in the clinical evaluation reported high rates of single session stone clearance for POCPS-guided EHL/LL (100% (Angsuwatcharakon et al., 2019) and 92.3% (Li et al., 2021)).

As with other key economic analysis (Health Technology Wales, 2020), the only clinical efficacy data available was for the initial extraction attempt of a difficult stone. As the efficacy rates for repeated procedures are not known, it was assumed that the accuracy of all repeat procedures would be equal to the success rate of the initial extraction attempt reported in Angsuwatcharakon et al. (2019).

The commentary highlighted that the economic model developed by Health Technology Wales noted that the success rate of repeat procedures is unknown, and as such, the accuracy of all repeated procedures is equal to previous procedures. This assumption is appropriate for the model presented in the ADAR. To note, this assumption is conservative and favours the comparator (Health Technology Wales, 2020).

As verified by the 2021 Advisory Board, POCPS-guided EHL/LL has increasing incremental efficacy with the increasing difficulty of stones. Therefore, the results in this analysis may underestimate the comparative effectiveness of POCPS-guided EHL/LL, as the increasing difficulty of stone extraction at follow up procedures is not captured.

This economic model presents a stepped evaluation of the cost of the proposed medical service (POCPS) and comparator medical service (ERCP/ laparoscopic choledochotomy). The first step considers MBS costs, and the second step includes additional costs to the hospital budget (consumables, capital, and other hospital costs).

The commentary noted the cost weightings considered for surgery include complexities associated with pancreas and liver. Surgeries for conditions associated with the pancreas and liver are likely to be more complex than surgeries for the removal of difficult biliary stones and as such, price weightings may be overestimated.

### *Investigative application*

The proportion of patients with indeterminate results was a key clinical input for the analysis. The results used in the base case analysis were extracted from the key RCT identified in the clinical evaluation (Gerges et al., 2020), in which the number of indeterminate results for the proposed and comparator test (13.3% vs 25.9%) were directly compared. As summarised in the clinical evaluation, the reported 12% reduction in indeterminate values associated with the use of POCPS is likely to be highly conservative given that patients were evaluated at the index ERCP procedure and that the impact of POCPS-guided visualisation was not accounted for.

The model is segmented based on the true condition of the patient (malignant vs benign). The proportion of patients in each arm of the decision analysis tree is based on the prevalence of malignancy for patients with indeterminate biliary strictures. The prevalence of malignancy was estimated to be 63% based on data from studies included in Navaneethan et al. (2015b) which enrolled patients with indeterminate strictures based on inconclusive results from a prior ERCP.

This prevalence value was consistent with the HTW Evidence Appraisal Report (Health Technology Wales, 2020) and was validated by the 2021 Advisory Board.

Results used in the base case analysis for POCPS sensitivity and specificity were extracted from Minami et al. (2021) (96.5%, 91.7%). Although a large range of studies reported on POCPS test accuracy, Minami et al. (2021) was the only study evaluating the combined sensitivity and specificity of POCPS-guided visualisation and POCPS-guided biopsy. According to the 2021 Advisory Board, standard clinical practice in Australia uses the combined results of visualisation and biopsy to inform the diagnosis of an indeterminate biliary stricture. Therefore, the results presented by Minami et al. (2021) (96.5% sensitivity and 91.7% specificity) are the best reflection of test accuracy observed in Australian clinical practice.

The study Minami et al. (2021) was considered as having low risk of bias in the clinical evidence section in the ADAR. This was amended to reflect a status of 'at risk of bias' due to a high risk of bias identified in the domain of reference standard. As such, there is a degree of uncertainty around the testing accuracy of POCPS used in the model.

Results used in the base case analysis for ERCP sensitivity and specificity were extracted from Navaneethan et al. (2015a). According to Australian physicians, the combined pooled sensitivity and specificity results for ERCP-guided brush cytology and ERCP-guided intraductal biopsy are the best reflection of clinical practice in Australia (59.4% sensitivity and 100% specificity). These results are however likely to be an overestimation of what is observed in clinical practice, as ERCP-guided brush cytology and ERCP-guided intraductal biopsy were evaluated at the index ERCP procedure.

Given the management of strictures is highly dependent on local clinical practice, all patient management inputs were derived from the 2021 Advisory Board.

The commentary noted that the MBS fees for POCPS was poorly justified. The commentary considered that it is unclear whether the cost of POCPS has been appropriately estimated as the inputs for the calculations amounting to 128% and 63% are unclear.

Capital and consumable equipment for ERCP, POCPS and laparoscopic choledochotomy in both therapeutic and investigative applications have been assessed in comparison with equipment outlined in other studies. It is not certain that the equipment listed in the ADAR is appropriate given information in these studies is varied and subject to individual preferences of hospitals, health professionals and countries. The applicant clarified that differences in the required equipment were due to differences in the legacy and digital systems.

## **Results of the base case**

The commentary considered the costs were appropriately captured in the ADAR including the total and repeat MBS costs of ERCP, POCPS and laparoscopic choledochotomy, the cost of consumables and capital equipment and additional hospital costs, and downstream costs of surgery. Private hospital cost weightings were used to quantify additional hospital costs for the removal of difficult biliary stones and the diagnosis of intermediate biliary strictures, and include costs for accommodation, coronary care unit, hospital-in-the-home, intensive care unit, ward labour, pharmacy, prostheses and theatre per separation in private hospitals. While out of pocket costs and the impact of adverse events are considered they are not explicitly quantified in the ADAR.

### ***Therapeutic application***

The clinical and costs impacts of POCPS-guided EHL/LL are presented in Table 21. In the base case analysis for patients with difficult biliary stones, POCPS-guided EHL/LL was associated with an incremental saving of \$127.97 per successful stone removal (Table 21).

The cost of the initial procedure is \$865,716.00 for therapeutic POCPS-guided EHL/LL compared with \$834,489.50 for the weighted comparator (ERCP-guided mechanical lithotripsy and laparoscopic choledochotomy) based on a patient cohort of 1000 for each arm. Therapeutic POCPS-guided EHL/LL successfully removed stones in 67 more patients than ERCP-guided mechanical lithotripsy and avoided repeated endoscopic procedures and surgeries in 84 and 409 patients, respectively. When including the costs to the hospital budget, the saving per successful stone removal was \$2,484.77.

**Table 21 Summary of clinical and cost impacts in the economic evaluation of therapeutic POCPS (per 1,000 procedures)**

Type of resource item	POCPS	ERCP /laparoscopic choledochotomy	Incremental
<b>Clinical outcomes</b>			
Number of patients with stones successfully removed (initial and follow up procedures)	972	905	67
Total number of repeated endoscopic procedures (POCPS/ERCP)	167	251	-84
Total number of endoscopic procedures (POCPS/ERCP) conversion to laparoscopic choledochotomy	28	94	-66
Total number of laparoscopic choledochotomy procedures performed	28	437	-409
<b>Cost outcomes (step 1 – MBS costs)</b>			
Total cost of initial procedure	\$865,716.00	\$834,489.50	\$31,226.50
Total cost of repeated endoscopic procedures (POCPS/ERCP)	\$250,209.38	\$292,806.11	-\$42,596.73
Total cost of conversion to laparoscopic choledochotomy	\$49,024.68	\$165,622.43	-\$116,597.75
Total cost of extraction of difficult biliary stones	\$1,164,950.06	\$1,292,918.04	-\$127,967.98
<b>Cost per patient with difficult biliary stones</b>	<b>\$1,164.95</b>	<b>\$1,292.92</b>	<b>-\$127.97</b>
<b>Cost per successful stone removal</b>	<b>\$1,147.94</b>	<b>\$1,245.21</b>	<b>Dominant</b>
<b>Cost outcomes (step 2 – including capital, consumables and additional hospitalisation costs)</b>			
Total cost of initial procedure	\$12,310,352.67	\$13,008,929.10	-\$698,576.43
Total cost of repeated endoscopic procedures (POCPS/ERCP)	\$2,229,933.70	\$2,901,142.11	-\$671,208.40
Total cost of conversion to laparoscopic choledochotomy*	\$567,065.01	\$1,915,743.00	-\$1,348,677.99
Total cost of extraction of difficult biliary stones	\$15,107,351.38	\$17,825,814.20	-\$2,718,462.82
<b>Cost per patient with difficult biliary stones</b>	<b>\$15,107.35</b>	<b>\$17,825.81</b>	<b>-\$2,718.46</b>
<b>Cost per successful stone removal (initial and follow up procedures)</b>	<b>\$14,957.43</b>	<b>\$17,574.27</b>	<b>Dominant</b>

Source: Pre-MSAC response with corrected capital cost per service.

Abbreviations: ERCP = endoscopic retrograde cholangiopancreatography-guided mechanical lithotripsy; POCPS = single operator, single use, peroral cholangiopancreatotomy electrohydraulic or laser lithotripsy

\*It is noted that the total cost of conversion to laparoscopic choledochotomy makes up a large proportion of the total per patient cost and the costs of successful stone removal.

The cost of capital for ERCP and POCPS in both therapeutic and investigative applications is calculated using the forgone capital return of a duodenoscope and spyglass equipment (DS digital controller for both applications, with the addition of an Autolith Generator in the therapeutic application) respectively, reported based on cost per service. The corrected capital cost for the therapeutic application (from the pre-MSAC response) been disaggregated in the table below.

**Table 22 Disaggregation of therapeutic capital cost per service**

Procedure	Item	Fee
ERCP	Reusable duodenoscope (capital)	\$35,000.00
	Life years	3
	Forgone capital return	1750
	Total opportunity cost of capital	\$13,416.67
	Duodenoscope cost per service	\$13.42
	Total cost per service	\$13.42
POCPS	SpyGlass DS Digital Controller (capital)	\$redacted
	Autolith Generator	\$redacted
	SpyGlass DS Digital Controller Life years	5
	Autolith Generator Life years	5
	Forgone capital return	\$46,600.00
	Total opportunity cost of capital	\$233,000.00
	POCPS cost per service	\$6.55
	Total cost per service	\$46.17

Abbreviations: ERCP = endoscopic retrograde cholangiopancreatography; POCPS = single operator, single use, peroral cholangiopancreatotomy  
 Source: Attachment 3.1(Therapeutic CEA spreadsheet) – pre-MSAC response  
 Note: The pre-MSAC response corrected the cost of the controller which was incorrectly stated as \$redacted instead of \$redacted and hence was overestimated. This decreased the cost of POCPS

The commentary highlighted that PASC noted that POCPS is currently performed at a limited number of public hospitals and not commonly performed in the private sector due to the high cost of equipment (Ratified PICO, page 9). Similarly, using DRG H02B and H01C as a proxy for private and public hospital separations, the procedure is likely to be performed in public hospitals (2606 and 572 separations in public and private hospitals in 2018-19 respectively). As such, it may be incorrect to assume that capital and consumable costs will be funded primarily by private health insurers, instead of the government health budgets.

To provide a suite of metrics for MSAC review, several sensitivity analyses were performed to adjust for the range of clinical efficacy results reported in the clinical evaluation.

For therapeutic POCPS, alternative clinical inputs included:

- Single session stone clearance values reported in the RCT by Angsuwatcharakon et al. (2019)
- Single session stone clearance upper values reported in indirect comparative evidence (pooled digital POCPS vs results reported in Angsuwatcharakon et al. (2019)
- Single session stone clearance lower values reported in indirect comparative evidence (pooled legacy POCPS vs results reported in Cipolletta et al. (1997)).

The main source of uncertainty for the utilisation of POCPS is its uptake rate in the ERCP market. There is no definitive epidemiology on patients with difficult biliary stones, therefore, three approaches were presented in the Ratified PICO (page 17). There is no definitive epidemiology

on patients with difficult biliary stones, therefore, three approaches were presented in the Ratified PICO (1673 Ratified PICO, page 17).

When considering the total incremental cost per patient, POCPS remained cost saving in all scenarios. The result was most sensitive to single session stone clearance. In the scenario where POCPS clearance rate was 100% (Angsuwatcharakon et al., 2019), the cost effectiveness of POCPS increased 234% to -\$427.20 per patient. Similarly, when the clearance rate for ERCP was decreased to 25.6% (and POCPS decreased to 73.1%), the incremental cost effectiveness of POCPS was -\$633.54 per initial procedure.

### **Sensitivity analysis**

The commentary has repeated the sensitivity analysis for the therapeutic and investigative application of POCPS using inputs provided in the CEA model. Each parameter has been adjusted by  $\pm 20\%$  their original value to assess the impact to the model and identify the main drivers. The sensitivity analysis' in the ADAR are largely aligned with the commentary's analysis (with the addition of consumables and capital and additional hospital costs in the HTA sensitivity analysis). The commentary considered the biggest driver of the model to be single session stone clearance. The biggest drivers of the MBS sensitivity analysis were single session stone clearance for POCPS, ERCP, and laparoscopic choledochotomy, which is in line with the sensitivity analysis provided in the ADAR. The cost of treatment (POCPS), and MBS cost of ERCP and laparoscopic choledochotomy were major drivers of the model, as presented in the ADAR. Other drivers that may be worth considering are the proportion of use of ERCP and choledochotomy for difficult stones, and the percentage of procedures repeated after one failed stone clearance for ERCP

Overall, the commentary considered the sensitivity analysis in the ADAR reasonably captured the major drivers of the model. Although there is a degree of uncertainty surrounding the accuracy of calculations for the cost of POCPS (and since this is the fourth and second largest driver in the HTA and ADAR model respectively) any discrepancies in cost will have a large effect on the outcomes of the model. The commentary considered this fee should be further justified to ensure the accuracy of the outcomes.

A separate analysis for the therapeutic application of POCPS was conducted with the inclusion of consumables, capital, and additional hospital cost. Key inclusions in this model that were not included in the MBS cost sensitivity analysis are the sum of consumable and capital costs of POCPS, laparoscopic choledochotomy and ERCP.

Additional sensitivity analyses performed by ESC are presented in Table 23. ESC considered comparisons where ERCP was the only comparator (laparoscopic choledochotomy third line) and modelling non-inferior effectiveness between POCPS and laparoscopic choledochotomy would be informative.

**Table 23: Sensitivity analyses performed for ESC**

Parameter	Incremental effectiveness	Incremental cost	ICER (per successful stone removal)
<b>Base case</b>	+67	-\$2,484,771	Dominant
ERCP as only comparator	+113	-\$3,425,298	Dominant
POCPS non-inferior to laparoscopic choledochotomy (83% clearance)	+76	-\$3,425,298	Dominant
<b>+ MBS cost of POCPS = ERCP</b>			
Base case (revised fee)	+67	-\$3,051,952	Dominant
ERCP as only comparator	+113	-\$1,403,591	Dominant
POCPS non-inferior to laparoscopic choledochotomy (83% clearance)	+76	-\$3,992,478	Dominant

Source: Calculated for the ESC report using capital costs presented in the ADAR

Abbreviations: ERCP = endoscopic retrograde cholangiopancreatography; POCPS = single operator, single use, peroral cholangiopancreatography

### **Investigative application**

The clinical and costs impacts of POCPS-guided visualisation and biopsy are presented in Table 24.

In the base case analysis for patients with difficult biliary stones, POCPS-guided visualisation/biopsy was associated with an incremental saving of \$2,568.39 per correctly diagnosed patient. When including the costs to the hospital budget, the incremental cost per correctly diagnosed patient was \$6,807.96. The commentary considered that is a reasonable cost given that earlier diagnosis of malignancy increases the proportion of patients eligible for surgical resection, which remains the only means of cure for biliary tract cancer (Fairweather et al., 2016).

**Table 24 Summary of clinical and cost impacts in the economic evaluation of investigative POCPS (per 1,000 procedures)**

Type of resource item	POCPS	ERCP	Incremental
<b>Clinical outcomes</b>			
Number of patients correctly diagnosed	909	653	256
Number of repeated ERCP procedures	98	195	-98
Number of unnecessary surgeries performed	17	43	-26
Number of malignant patients diagnosed as benign	18	228	-210
<b>Cost outcomes (step 1 – MBS costs)</b>			
Cost of initial test	\$1,213,609.25	\$1,022,998.25	\$190,611.00
Cost of retesting	\$118,326.90	\$199,484.66	-\$81,157.76
Cost of unnecessary surgery	\$491,118.87	\$1,257,829.62	-\$766,710.75
Total cost of diagnosis	\$1,823,055.02	\$2,480,312.53	-\$657,257.51
Cost of diagnosis per patient tested	\$1,823.06	\$2,480.31	-\$657.26
Cost per correctly diagnosed patient (initial cost only)	\$1,335.81	\$1,567.54	\$744.86
<b>Cost per correctly diagnosed patient (total cost of diagnosis)</b>	<b>\$2,006.63</b>	<b>\$3,800.58</b>	<b>-\$2,568.39</b>
<b>Cost outcomes (step 2 – including capital, consumables, and additional hospitalisation costs)</b>			

Type of resource item	POCPS	ERCP	Incremental
Cost of initial test	\$15,262,745.92	\$12,101,884.92	\$3,160,861.00
Cost of retesting	\$1,488,117.73	\$2,359,867.56	-\$871,749.83
Cost of unnecessary surgery	\$491,118.87	\$1,257,829.62	-\$766,710.75
Total cost of diagnosis	\$17,241,982.51	\$15,719,582.10	\$1,522,400.42
Cost of diagnosis per patient tested	\$17,241.98	\$15,719.58	\$1,522.40
Cost per correctly diagnosed patient (initial cost only)	\$16,799.64	\$18,543.73	\$12,351.81
<b>Cost per correctly diagnosed patient (total cost of diagnosis)</b>	<b>\$18,978.18</b>	<b>\$24,087.13</b>	<b>\$5,949.14</b>

Abbreviations: ERCP = endoscopic retrograde cholangiopancreatography; POCPS = single operator, single use, peroral cholangiopancreatography  
Source: Pre-MSAC response with corrected capital cost per service.

The commentary considered that this service is likely to be performed in public hospitals where hospitals absorb the capital and consumable costs.

The cost of capital for ERCP and POCPS in both therapeutic and investigative applications is calculated using the forgone capital return of a duodenoscope and spyglass equipment (DS digital controller for both applications, with the addition of an Autolith Generator in the therapeutic application) respectively, reported based on cost per service. The capital cost has for the investigative application been disaggregated in the table below.

**Table 25 Disaggregation of investigative capital cost per service**

Service	Item	Fee
ERCP	Reusable duodenoscope (capital)	\$35,000.00
	Life years	3
	Forgone capital return	\$1,750.00
	Total opportunity cost of capital	\$13,416.67
	Duodenoscope cost per service	\$13.42
	Total cost per service	\$13.42
POCPS	SpyGlass DS Digital Controller (capital)	\$redacted
	SpyGlass DS Digital Controller Life years	5
	Forgone capital return	\$44,500.00
	Total opportunity cost of capital	\$222,500.00
	POCPS cost per service	\$4.45
	Total cost per service	\$35.67

Source: Attachment 3.2 (Investigative CEA spreadsheet) – pre-MSAC response

Note: The pre-MSAC response corrected the cost of the controller which was incorrectly stated as \$redacted instead of \$redacted and hence was overestimated. This decreased the cost of POCPS

Whilst not included in the cost effectiveness model, the commentary considered the outcomes of reduced repeated procedures to determine a definitive malignant diagnosis can be considered as additional benefits with long-term impacts on health system costs and patient safety.

### Sensitivity analysis

The ADAR presented several sensitivity analyses to adjust for the range of clinical efficacy results reported in the clinical evaluation. The results presented in the ADAR were based on total MBS costs of diagnosis and did not include hospital, consumable and capital costs. The ADAR's sensitivity analyses demonstrated that POCPS was dominant for all the analyses. The results of the key sensitivity analysis based on the total cost (including hospital, consumable and capital costs) are presented in Table 26.

**Table 26: Sensitivity analyses for biliary strictures (per additional correctly diagnosed patient – total cost)**

Parameter	Incremental effectiveness	Incremental cost	ICER (per correctly diagnosed patient)
<b>Base case</b>	+256	\$1,742,175	\$6,808
MBS cost POCPS = MBS cost of ERCP	+256	\$1,479,641	\$5,782
<b>Prevalence of malignancy</b> (base case 63%)			
Lower prevalence (50%)	204	\$1,472,790	\$7,230
Higher prevalence (70%)	284	\$1,887,228	\$6,645
<b>Diagnostic performance</b> (Base case POCPS: Sens = 97%, Spec =92%; ERCP: Sens =59%, Spec = 99%)			
POCPS: Sens = 68%, Spec = 63% (Gerges 2020) ERCP : Sens = 22%; Spec = 85% (Gerges 2020)	+232	\$1,742,175	\$7,505
POCPS: Sens. 77%, Spec. 100% (Draganov 2012) ERCP: Sens. 5.8%, Spec. 100% (Draganov 2012 ERCP-BC)	+457	\$1,742,175	\$3,812
POCPS: Sens. 77%, Spec. 100% (Draganov 2012) ERCP: Sens. 29.4%, Spec. 100% (Draganov 2012 ERCP-IB)	+325	\$1,742,175	\$5,352
<b>Patients receiving correct diagnosis</b> (Base case Gerges (2020): POCPS: 87% ERCP: 74%)			
POCPS: 91.7% ERCP: 83.3% (Draganov 2012 ERCP-BC)	+235	\$2,408,395	\$10,245
POCPS: 91.7% ERCP: 73.1% (Draganov 2012 ERCP-IB)	+279	\$842,771	\$3,026

Source: Calculated for the ESC report using Table 110 of the ADAR using the cost of capital from the ADAR

Abbreviations: BC = brush cytology; ERCP = endoscopic retrograde cholangiopancreatography; IB = intraductal biopsy; POCPS = single operator, single use, peroral cholangiopancreatography; sens = sensitivity; spec = specificity

The commentary considered the main drivers of the investigative model included the proportion of people that receive a diagnosis for POCPS and ERCP. The accuracy and cost of the diagnostic test and proportion of people who must retest after failed ERCP diagnostic attempts are also important factors in the model for both ERCP and POCPS. The prevalence of malignancy is among the largest drivers of the model which is also consistent with the ADAR sensitivity analysis.

The commentary considered that there is a degree of uncertainty surrounding the accuracy of calculations for the cost of POCPS, and since this noted as one of the top 10 drivers and any discrepancies in cost will have a large effect on the outcomes of the model. The commentary considered fee should be further justified to ensure the accuracy of the outcomes.

The economic analysis did not explore the management of correct or incorrect diagnosis due to the complexity and uncertainty of the downstream costs for multiple potential conditions. However, to emphasise the impact of misdiagnosing malignancies, a terminal care cost was applied to all patients with malignant strictures diagnosed as benign.

## 14. Financial/budgetary impacts

A mixed market share and epidemiological approach was adopted to inform the utilisation estimates and financial implication to the Government upon MBS listing of the two applications of POCPS in Australia. The MBS Statistics data published epidemiological data and the 2021 Advisory Board were used to estimate the number of POCPS services provided under the MBS for the removal of difficult biliary stones (therapeutic application) and for the diagnosis of indeterminate biliary strictures (investigative application). In addition to the budget impact to the MBS, this budget impact analysis also considers the financial implications to the hospital budget, including capital and consumable costs.

The commentary considered the financial estimates for therapeutic and investigative applications were appropriately addressed in the ADAR. Key assumptions and inputs for both applications have been assessed and are appropriate in respect to the available information. The main limitations were the uncertainty surrounding POCPS fee calculations and parameters based on expert opinion.

### **Selection of data sources**

The variables and associated data sources used to determine the utilisation and financial implication associated with a listing for therapeutic POCPS on the MBS are presented in Table 27.

**Table 27 Summary of data sources and parameter values applied in the utilisation and financial estimates for therapeutic POCPS**

Data	Value	Source	Justification
Procedure annual growth rate	3.74%	Medicare Statistics MBS Item Reports for 30484	Eligibility for POCPS is dependent on a prior ERCP. Therefore, the rate of growth for ERCP procedures (item 30484) is estimated to reflect the rate of growth of POCPS
Proportion of ERCP procedures undertaken to remove stones	45.50%	Testoni et al. (2010), 2021 Advisory Board	Estimated using values from an Italian multicentre study on 3,635 ERCP procedures, of which 45.5% were performed for choledocholithiasis. This value was deemed to be applicable to the Australian clinical setting by the 2021 Advisory Board
Proportion of stones which are unable to be removed by standard ERCP extraction techniques	10.00%	2021 Advisory Board, McHenry and Lehman (2006)	Patients with biliary stones are typically treated using conventional ERCP extraction techniques, however approximately 10% are to be unable to be removed. Biliary stones may be difficult to remove if they are impacted, lodged behind strictures, large in size (> 15 mm in diameter) or located in regions of the biliary tree which are difficult to target endoscopically (Aljebreen et al., 2014)
Proportion of ERCP procedures with stones unable to be extracted (difficult biliary stones)	4.55%	Calculated	Calculated based on the proportion of ERCP procedures undertaken to remove stones and the proportion of ERCP procedures with stones unable to be extracted (45.50% x 10.00%)
ERCP market share in the world w/o POCPS	66.67%	2021 Advisory Board	Based on clinical practice in Australia prior to the introduction of POCPS
Laparoscopic choledochotomy market share in the world w/o POCPS	33.33%	2021 Advisory Board	Based on clinical practice in Australia prior to the introduction of POCPS
POCPS uptake rate in ERCP market	2022: 20% 2023: 26% 2024: 34% 2025: 44% 2026: 58% 2027: 76%	BSC internal estimates	As POCPS is an adjunct to ERCP, POCPS is expected to have more traction in the ERCP market than in the laparoscopic choledochotomy market. Hence 2022 adoption is starting at 20% for ERCP compared to 3% for laparoscopic choledochotomy. Annual growth based on 31% compound annual growth for SpyGlass DS public adoption from 2015-2019
POCPS uptake rate in laparoscopic choledochotomy market	2022: 10% 2023: 13% 2024: 17% 2025: 22% 2026: 29% 2027: 39%	BSC internal estimates	POCPS uptake in laparoscopic choledochotomy market is expected to have less traction than in the laparoscopic choledochotomy market, hence 2022 adoption is starting at 10% compared to 20% for ERCP. Annual growth based on 31% compound annual growth for SpyGlass DS public adoption from 2015-2019

Cost and resource utilisation data have been extrapolated until 2027, using assumptions about the annual growth rate and uptake of POCPS in the ERCP market. Additionally, all current costs have been inflated to 2021. The commentary considered that this method is appropriate to determine future costs and utilisation.

The variables and associated data sources used to determine the utilisation and financial implication associated with a listing for investigative POCPS on the MBS are presented in Table 28.

**Table 28 Summary of key assumptions applied for utilisation and financial estimates for investigative POCPS**

Data	Value	Source	Justification
Procedure Annual Growth Rate	3.74%	Medicare Statistics MBS Item Reports for 30484	Eligibility for POCPS is dependent on inconclusive results from a prior ERCP. Therefore, the rate of growth for ERCP procedures (item 30484) is estimated to reflect the rate of growth of POCPS
Proportion of ERCP procedures undertaken to diagnose biliary strictures	23.20%	Testoni et al. (2010), 2021 Advisory Board	Estimated using values from an Italian multicentre study on 3,635 ERCP procedures, of which 23.20% were performed for malignant or benign biliary strictures. This value was deemed to be applicable to the Australian clinical setting by the 2021 Advisory Board
Proportion of biliary strictures which have inconclusive results	10.00%	2021 Advisory Board	As informed by the 2021 Advisory Board, ERCP fluoroscopic images are limited by their poor sensitivity resulting in up to 10% of strictures remaining indeterminate (i.e. no diagnosis is made)
Proportion of ERCP procedures resulting in inconclusive results for biliary strictures (i.e. inability to make a diagnosis)	2.32%	Testoni et al. (2010), 2021 Advisory Board	Calculated based on the proportion of ERCP procedures undertaken to diagnose biliary strictures and the proportion of biliary strictures which have inconclusive results (23.20% x 10.00%)
ERCP market share in the world w/o POCPS	100%	2021 Advisory Board	Based on clinical practice in Australia prior to the introduction of POCPS
POCPS uptake rate in ERCP market	2022: 13% 2023: 17% 2024: 22% 2025: 29% 2026: 39% 2027: 51%	BSC internal estimates	Indeterminate biliary strictures are expected to have less traction than difficult biliary stones, hence 2021 adoption is starting at 10% compared to 15% for difficult stones. Annual growth based on 31% compound annual growth for SpyGlass DS public adoption from 2015-2019

Abbreviations: BSC = Boston Scientific; DS = digital system; ERCP = endoscopic retrograde cholangiopancreatography-guided brush cytology/intraductal biopsy, MBS = Medicare Benefit Schedule; POCPS = single operator, single use peroral cholangiopancreatoscopy-guided visualisation/biopsy

Similar to the assumptions for the therapeutic procedure, the input for the proportion of procedures undertaken to diagnose biliary strictures is justified in the ADAR by an Italian multi-centre study (Testoni et al., 2010). While the clinical setting and proportion of patients presenting with choledocholithiasis may be different in the Australian clinical setting, the Advisory Board has supported the use of these values.

Cost and resource utilisation data have been extrapolated until 2027, using assumptions about the annual growth rate and uptake of POCPS in the ERCP market. Additionally, all current costs have been inflated to 2021. This method is appropriate to determine future costs and utilisation.

The calculations in Table 27 and Table 28 appear to be appropriate, given the 2021 Advisory Board suggested inputs are reflective of current health practice in Australia.

The ADAR considered the additional costs of POCPS are borne by hospitals and health funds, including capital equipment and consumable costs through contractual arrangements. The ADAR incorrectly overestimated the cost of capital as the cost of the controller was incorrectly entered as \$redacted instead of \$redacted. This was corrected in the pre-MSAC response.

While public hospitals receive almost all funding from state or federal governments (captured in public hospital NHDCDC Reports), private hospitals typically receive funding from a number of sources including private health insurers, directly from patients in the form of out-of-pocket fees, and from state or federal government funding. A proportion of the costs of POCPS and its comparators are borne by hospitals, including the cost of capital equipment and consumables. Additional costs covered under the hospital budget were estimated using the costs extracted from the Private Hospital Data Bureau 2016-17 Annual Report, which covers costs for accommodation, coronary care unit, hospital-in-the-home, intensive care unit, ward labour, pharmacy, prostheses and theatre per separation in private hospitals. The endoscopic clearance of difficult stones (POCPS and ERCP) was associated with major biliary tract procedures of minor complexity. In comparison laparoscopic choledochotomy for the removal of difficult biliary stone was associated with the weighted cost of major biliary tract procedures ranging from intermediate to major complexity as this is a more invasive procedure associated with significantly longer hospital stays (Li et al., 2021). The cost of consumables and capital were sourced from Boston Scientific internal data. No detailed estimate on the cost of capital and consumables for choledochotomy were available, therefore, the cost of this comparator to the hospital budget was conservatively estimated using the AR-DRG cost alone.

Additional costs consider major biliary tract procedures of minor complexity for ERCP/POCPS and major biliary tract interventions of major complexity and, major biliary tract interventions of intermediate complexity for laparoscopic choledochotomy. Pancreas and liver conditions are included in the consideration for these costs, and as such, the commentary considered the weighted index attributed to additional costs borne by hospitals may be overestimated.

The ADAR has considered the cost of hospitalisation for POCPS and ERCP with DRG H02C. Similarly, the hospital cost of laparoscopic choledochotomy has been considered in reference to DRGs H02A and H02B. While the mean length of stay for the above mentioned DRGs have been used in the model and is assumed to be equivalent in both the intervention and comparator arms, this could be a conservative measure as this is on the lower end of results presented in Li et al. (2021). The average length of stay for DRG H02C is 5.39 days and the length of hospitalisation for POCPS as reported in Li et al. (2021) is 5.65 days and 8.84 days for laparoscopic choledochotomy. While Li et al. (2021) is a Chinese study, it is one of two studies which reported length of hospitalisation. The other study, Angsuwatcharakon (2019) reports length of stay (1 day for POCPS and ERCP), but statistically does not make sense possibly due to rounding (lower confidence interval is the same as the mean length of hospitalisation). ESC advised that the length of stay for POCPS and ERCP is unlikely to be 5.39 days on average as many will be same-day procedures. ESC considered a length of stay of 5 days would only occur where patients experience complications.

### **Net financial impact**

The net financial impact of POCPS for therapeutic application is summarised in the Table 29, and further detailed in the sections below.

**Table 29: Net financial impact of POCPS for difficult biliary stones**

Parameter	Year 1 (2022)	Year 2 (2023)	Year 3 (2024)	Year 4 (2025)	Year 5 (2026)	Year 6 (2027)
<b>Estimated use and cost of POCPS for difficult biliary stones</b>						
People with difficult biliary stones <sup>a</sup>	399	413	429	445	462	479
ERCP for difficult biliary stones (67% of patients)	266	276	286	297	308	319
Surgery for difficult stones (33% of patients)	133	138	143	148	154	160
POCPS uptake (from ERCP)	20%	26%	34%	45%	59%	77%
POCPS uptake (from surgery)	10%	13%	17%	22%	29%	39%
POCPS services <sup>b</sup>	78	105	143	195	264	359
Cost to the MBS	\$55,309	\$75,163	\$102,143	\$138,809	\$188,637	\$256,351
<b>Change in use and cost of other health technologies</b>						
Change in use of ERCP <sup>c</sup>	-71	-97	-132	-179	-244	-331
Change in surgery	-14	-19	-25	-35	-47	-64
Change in conversions to surgery	-12	-16	-22	-30	-41	-56
Cost savings from reduced ERCP and surgery	-\$53,541	-\$72,760	-\$98,878	-\$134,372	-\$182,607	-\$248,157
<b>Net cost to the MBS</b>	<b>\$1,768</b>	<b>\$2,402</b>	<b>\$3,265</b>	<b>\$4,437</b>	<b>\$6,030</b>	<b>\$8,194</b>
<b>Change in hospital costs</b>						
POCPS <sup>d</sup>	\$891,800	\$1,211,924	\$1,646,962	\$2,238,162	\$3,041,582	\$4,133,401
ERCP and surgery	-\$908,302	-\$1,234,350	-\$1,677,438	-\$2,279,578	-\$3,097,865	-\$4,209,887
<b>Net hospital costs <sup>d</sup></b>	<b>-\$16,502</b>	<b>-\$22,426</b>	<b>-\$30,476</b>	<b>-\$41,416</b>	<b>-\$56,283</b>	<b>-\$76,486</b>

Abbreviations: ERCP = endoscopic retrograde cholangiopancreatography-guided mechanical lithotripsy; MBS = Medicare Benefit Schedule; POCPS = single operator, single use peroral cholangiopancreatotomy-guided electrohydraulic/laser lithotripsy

<sup>a</sup> Calculated as 4.55% of ERCP procedures

<sup>b</sup> 17% of initial POCPS procedures are repeated

<sup>c</sup> 17% of initial ERCP procedures are repeated

<sup>d</sup> Revised in the pre-MSAC response.

The MBS cost of POCPS for the removal of difficult biliary stones was estimated to be \$55,309 in 2022 increasing to \$256,351 in 2027. The financial impact of POCPS to the MBS was offset by changes in the utilisation of ERCP and laparoscopic choledochotomy. The estimated net cost to the MBS was \$1,768 in 2022 increasing to \$8,194 in 2027.

The net cost of POCPS to the hospital budgets was estimated to be -\$16,502 in 2022 increasing to -\$76,486 in 2027, including reductions in repeated procedures.

The net financial impact of POCPS for therapeutic application is summarised in the Table 30, and further detailed in the sections below.

**Table 30: Net financial impact of POCPS for indeterminate biliary strictures**

Parameter	Year 1 (2022)	Year 2 (2023)	Year 3 (2024)	Year 4 (2025)	Year 5 (2026)	Year 6 (2027)
<b>Estimated use and cost of POCPS for indeterminate biliary strictures</b>						
ERCP for indeterminate biliary strictures <sup>a</sup>	203	211	219	227	235	244
POCPS uptake	13%	17%	22%	29%	39%	51%
POCPS services <sup>b</sup>	29	40	54	73	100	135
Cost to the MBS	\$26,596	\$36,143	\$49,117	\$66,749	\$90,709	\$123,270
<b>Change in use and cost of other health technologies</b>						
Change in use of ERCP <sup>c</sup>	-32	-43	-59	-80	-109	-147
Change in surgery	-1	-2	-2	-3	-4	-5
Cost savings from reduced ERCP and surgery	-\$26,036	-\$35,382	-\$48,083	-\$65,343	-\$88,799	-\$120,674
<b>Net cost to the MBS</b>	<b>\$560</b>	<b>\$761</b>	<b>\$1,034</b>	<b>\$1,406</b>	<b>\$1,910</b>	<b>\$2,596</b>
<b>Change in hospital costs</b>						
POCPS (\$14,049 per service) <sup>d</sup>	\$410,513	\$557,873	\$758,129	\$1,030,270	\$1,400,100	\$1,902,686
ERCP (\$11,079 per service)	-\$352,482	-\$479,011	-\$650,958	-\$884,629	-\$1,202,179	-\$1,633,718
<b>Net hospital costs <sup>d</sup></b>	<b>\$58,031</b>	<b>\$78,862</b>	<b>\$107,171</b>	<b>\$145,642</b>	<b>\$197,922</b>	<b>\$268,968</b>

Abbreviations: ERCP = endoscopic retrograde cholangiopancreatography-guided mechanical lithotripsy; MBS = Medicare Benefit Schedule; POCPS = single operator, single use peroral cholangiopancreatography-guided electrohydraulic/laser lithotripsy

<sup>a</sup> 2.32% of forecast ERCP procedures.

<sup>b</sup> 10% of patients require repeat POCPS

<sup>c</sup> 19.5% of patients require repeat ERCP

<sup>d</sup> Revised in the pre-MSAC response.

The cost of POCPS for the diagnosis of indeterminate biliary strictures to the MBS was estimated to be \$26,596 in 2022 increasing to \$123,270 in 2027. The net financial impact of POCPS offset by changes in the utilisation of ERCP and surgical resection, resulting in an estimated net cost to the MBS of \$560 in 2022 increasing to \$2,596 in 2027. The commentary considered these results show how the introduction of POCPS has a negligible impact on the overall MBS budget.

The total cost of POCPS for the diagnosis of indeterminate biliary strictures to the hospital budget was estimated to be \$410,513 in 2022 increasing to \$1,902,686 in 2027. When considering the offset in costs of the comparator technology, the net cost of POCPS to the hospital budget was estimated to be \$58,031 in 2022 increasing to \$268,968 in 2027.

## Sensitivity analysis

### *Therapeutic application*

Table 31 presents the results of the sensitivity analyses for the therapeutic application. The main source of uncertainty for the utilisation of POCPS is its uptake rate in the ERCP market. There is no definitive epidemiology on patients with difficult biliary stones, therefore, three approaches were presented in the Ratified PICO (page 17). The chosen assumed that 45.5% of all ERCP procedures (MBS item 30484) were conducted to remove biliary stones, of which 10% of these stones were unable to be extracted during a prior ERCP (i.e. 4.55% of all current ERCP

procedures would be eligible for POCPS). This method relied on estimates given by physicians at the 2021 Advisory Board. Using these assumptions, the application estimated a likely population of 357 patients that will use POCPS for the removal of difficult biliary stones (Ratified PICO 1673). The commentary considered that this approach is appropriate given it is the more conservative method to identify costs to MBS.

ESC requested further sensitivity analyses examining different growth rates for ERCP and laparoscopic choledochotomy as POCPS is claimed to have superior effectiveness compared with ERCP but non-inferior effectiveness compared with laparoscopic choledochotomy. Assuming lower market growth from laparoscopic choledochotomy and higher market growth ERCP, separately, increased costs to the MBS. Reducing the MBS fee for POCPS to be the same as the fee for ERCP resulted in net savings to the MBS.

**Table 31 Sensitivity analysis: Net financial implications of POCPS to the MBS for patients with difficult biliary stones (POCPS minus ERCP and choledochotomy offsets)**

2022	2023	2024	2025	2026	2027
<b>Base case</b>					
\$7,616.62	\$10,350.72	\$14,066.25	\$19,115.53	\$25,977.32	\$35,302.25
<b>Change in single session stone clearance (base case POCPS : 83.3% ERCP: 62.5%)</b>					
POCPS : 100% , ERCP: 62.5% (Angsuwatcharakon et al. (2019)					
-\$5,809.64	-\$7,895.10	-\$10,729.16	-\$14,580.54	-\$19,814.43	-\$26,927.10
POCPS: 82.3%, ERCP: 62.3% (Upper values from indirect digital POCs comparative evidence and Chang 2005)					
\$7,014.25	\$9,532.11	\$12,953.79	\$17,603.74	\$23,922.85	\$32,510.30
POCPS: 73.1%, ERCP: 25.6%(Lower values from indirect legacy POCs comparative evidence and Cipolletta 1997)					
-\$1,085.60	-\$1,475.29	-\$2,004.87	-\$2,724.55	-\$3,702.56	-\$5,031.65
<b>Market uptake and growth</b>					
Higher ERCP market uptake (30%, base case 20%)					
\$15,233.27	\$20,701.46	\$28,132.55	\$38,231.12	\$51,954.72	\$70,604.60
Lower ERCP market uptake (10%, base case 20%)					
-\$0.02	-\$0.03	-\$0.04	-\$0.06	-\$0.08	-\$0.11
Higher uptake (20%) from laparoscopic choledochotomy market uptake (base case 10%)					
-\$0.05	-\$0.06	-\$0.08	-\$0.12	-\$0.16	-\$0.21
Lower market growth rate (3.69%, base case 3.74%)					
\$7,606.12	\$10,331.68	\$14,033.93	\$19,062.83	\$25,893.79	\$35,172.54
Lower growth in laparoscopic choledochotomy market share (16%, base case, 31%)					
\$7,616.62	\$11,575.43	\$17,198.00	\$25,129.68	\$36,256.97	\$51,796.03
Higher growth in ERCP market share (37.2%, base case 31%)					
\$7,616.62	\$11,330.48	\$16,792.20	\$24,804.74	\$36,533.59	\$53,668.39
<b>Eligible population (base case: MBS data + advisory board)</b>					
SA8: AIHW procedure codes (larger population)					
\$4,578.45	\$6,174.25	\$8,326.26	\$11,228.35	\$15,141.95	\$20,419.62
SA9: MBS co-claiming for ERCP and extraction of biliary calculus (smaller population)					
\$554.16	\$750.98	\$1,016.58	\$1,374.68	\$1,857.10	\$2,506.53
<b>MBS costs</b>					
<b>Higher MBS cost of choledochotomy (\$1,380.75, base case \$1,371.65)</b>					
\$7,522.50	\$10,222.80	\$13,892.42	\$18,879.31	\$25,656.30	\$34,865.99
<b>POCPS MBS fee same as ERCP (\$379.70, base case \$865.72)</b>					
-\$20,642.60	-\$28,052.55	-\$38,122.41	-\$51,806.99	-\$70,403.84	-\$95,676.30
<b>Multivariate analysis: POCPS MBS fee same as ERCP + higher growth in ERCP market share + lower growth from laparoscopic choledochotomy market share</b>					
-\$20,642.60	-\$26,393.34	-\$33,986.36	-\$44,084.14	-\$57,606.38	-\$75,834.17

Source: Table 151 of the ADAR and calculated following ESC.

Abbreviations: MBS = Medicare Benefit Schedule; POCPS = single operator, single use peroral cholangiopancreatography; SA = sensitivity analysis

### **Investigative application**

Values tested in the sensitivity analysis are presented in Table 32. The main source of uncertainty for the utilisation of POCPS is the number of patients with indeterminate biliary strictures. There is no definitive epidemiology on patients with indeterminate biliary strictures,

therefore, two approaches were presented in the Ratified PICO (Ratified PICO 1673, page 7). The chosen approach assumed that 23.2% of all ERCP procedures (MBS item 30484) were conducted to diagnose biliary strictures, of which 10% of these produced inconclusive results (i.e. 2.32% of all current ERCP procedures would be eligible for POCPS). This method relied on clinician estimates at the 2021 Advisory Board.

Although there is uncertainty around POCPS utilisation using clinician estimates, the commentary considered that this method is appropriate given that the proportion of ERCP procedures conducted to diagnose biliary strictures is underpinned by evidence from Testoni (2010), and due to the potential to underestimate the population for POCPS using the alternative method. All other scenarios had a minor impact on the financial estimates (Table 32).

**Table 32 Sensitivity analysis: Net financial implications of POCPS to the MBS patients with indeterminate biliary strictures (POCPS minus ERCP offsets)**

2022	2023	2024	2025	2026	2027
\$2,186.58	\$2,971.49	\$4,038.14	\$5,487.69	\$7,457.57	\$10,134.58
<b>Proportion receiving a diagnosis (base case POCPS: 87%, ERCP: 74% - Gerges (2020))</b>					
POCPS: 91.7% ERCP: 83.3% (Draganov (2012) POCPS vs ERCP-BC)					
\$2,757.09	\$3,746.79	\$5,091.76	\$6,919.52	\$9,403.37	\$12,778.85
POCPS: 91.7% ERCP: 73.1% (Draganov (2012) POCPS vs ERCP-IB)					
\$1,194.48	\$1,623.25	\$2,205.94	\$2,997.80	\$4,073.90	\$5,536.28
<b>POCPS annual growth in uptake rate in ERCP market (base case 31%)</b>					
Increase POCPS uptake in ERCP (40%)					
\$2,336.80	\$3,393.81	\$4,928.92	\$7,158.41	\$10,396.36	\$15,098.93
Decrease POCPS uptake in ERCP (10%)					
\$1,836.06	\$2,095.16	\$2,390.81	\$2,728.19	\$3,113.18	\$3,552.50
<b>Lower growth of ERCP on the MBS (3.69%, base case 3.74%)</b>					
\$2,183.50	\$2,965.90	\$4,028.66	\$5,472.23	\$7,433.06	\$10,096.52
<b>Indeterminant biliary strictures population (base case : 2.23% of ERCP procedures on MBS - 203 patients in 2022)</b>					
Smaller population (only where ERCP is co-claimed with biopsy, 50 patients in 2022)					
\$534.91	\$726.92	\$987.86	\$1,342.47	\$1,824.36	\$2,479.24
<b>Larger population (4.20% of ERCP procedures on MBS - 406 patients in 2022)</b>					
\$4,373.16	\$5,942.97	\$8,076.28	\$10,975.38	\$14,915.15	\$20,269.15
<b>POCPS MBS fee = ERCP MBS fee</b>					
-\$3,055.70	-\$4,152.58	-\$5,643.21	-\$7,668.92	-\$10,421.79	-\$14,162.83

Abbreviations: ERCP = endoscopic retrograde cholangiopancreatography-guided brush cytology/ intraductal biopsy; MBS = Medicare Benefits Schedule; POCPS = single operator, single use peroral cholangiopancreatography-guided visualisation/biopsy

## 15. Other relevant information

Nil

## 16. Key Issues from ESC to MSAC

ESC key issue	ESC advice to MSAC
Item descriptor and MBS fee.	The descriptor should include the frequency rule (as per the Ratified PICO) and multiple operation rule. ESC considered that insufficient rationale had been provided to support the higher MBS fees for POCPS. ESC noted that POCPS involves the use of an additional catheter during an endoscopic retrograde cholangiopancreatography (ERCP). Currently, ERCP has a flat MBS fee irrespective of complexity. ESC considered the diagnostic item should be under MBS category 3 (therapeutic procedures) and subject to the multiple operation rule.
Comparative safety	The direct comparative evidence consisted of small studies that lacked systematically collected information on harms and therefore data on harms is lacking. ESC considered more detailed adverse event data from the indirect non-comparative studies could support the claim of non-inferior safety. These data are important as there are known safety issues with this procedure (e.g. pancreatitis and cholangitis).
Quality of evidence	The direct comparative evidence mostly consisted of small studies derived from different populations as some participants had not failed prior ERCP as per the PICO.
Evidence for biliary stones	ESC had low confidence in the estimated benefit as the key study comparing POCPS with ERCP was small and had a high risk of bias for several reasons including practitioners' potential preference for POCPS with laser lithotripsy. The results may not be fully applicable because patients had stones in the common bile duct whereas POCPS may be used for more difficult stones.  ESC and the pre-ESC response accepted the revised clinical claim that POCPS was non-inferior to laparoscopic choledochotomy for difficult biliary stones.
Evidence for biliary strictures	ESC had low confidence in the estimated benefit of POCPS for biliary strictures (reported as superior sensitivity, fewer indeterminate results). This was due to the small direct studies where the reference standard for diagnosis of cancer (including surgical specimens, additional ERCPs) was variably applied to patients in the studies. The evidence to support a reduction in future procedures was lacking, as Gerges (2020) suggested patients undergo the same number of procedures to obtain a diagnosis.
Economic evaluation for biliary stones	ESC considered that it may be reasonable to model superior effectiveness for POCPS compared to ERCP and non-inferior effectiveness compared with laparoscopic choledochotomy. Further sensitivity analyses using ERCP as the only comparator (laparoscopic choledochotomy third line) and reducing the POCPS MBS fee to the ERCP MBS fee resulted in dominant incremental cost-effectiveness ratios (ICERs).
Economic evaluation for biliary strictures	There is uncertainty in the clinical inputs to the model arising from uncertainties in the clinical evidence. The ICERs become dominant in the stepped economic analysis when including the costs of unnecessary surgery for patients with benign conditions (not cancer) and the cost of unnecessary treatment for patients with incorrect diagnoses. Further sensitivity analysis using the same MBS cost for POCPS and ERCP also resulted in dominant ICERs.

ESC key issue	ESC advice to MSAC
Net costs to the MBS	The estimated net costs to the MBS were small– less than \$50,000 per year for the therapeutic application and less than \$5,000 per year for the investigative application. Reducing the MBS fees for POCPS to the same as ERCP resulted in net savings (as currently it is 2-3 times the cost of ERCP).
Substantial capital and consumable costs	There are very high capital and equipment/consumables costs for POCPS. The ADAR considered these costs would be reimbursed in the private sector by health insurance and absorbed by hospital budgets. It was unclear whether this would be the case as this procedure would most commonly be performed in the public sector. It is uncertain what the likely out-of-pocket costs may be for consumers.

## ESC discussion

ESC noted that this applicant-developed assessment report (ADAR) was for Medicare Benefits Schedule (MBS) listing of single operator, single use, peroral cholangiopancreatography (POCPS) for diagnosis of indeterminate biliary strictures and removal of difficult biliary stones. ESC noted that there is a single POCPS device on the market, and that the service is only available at limited public hospitals in Australia.

ESC noted that this application proposes two new MBS listings of single operator, single use POCPS for:

- diagnosis of indeterminate biliary strictures (diagnostic) following unsuccessful endoscopic retrograde cholangiopancreatography (ERCP)
- POCPS-guided electrohydraulic/laser lithotripsy for removal of difficult biliary stones (therapeutic) following unsuccessful ERCP-guided balloon/basket and/or lithotripsy with sphincterotomy.

ESC advised that POCPS for diagnosis should be considered a second line procedure after an initial ERCP and histopathology are inconclusive, and where clinically indicated. The procedural outcome from the initial ERCP procedure determines eligibility for POCPS.

ESC noted that the pre-ESC response clarified that the item descriptors should be subject to the multiple operation rule and the claiming limits proposed in the Ratified PICO and the commentary. ESC advised that the item descriptor should note that MBS item 30450 (extraction of biliary calculus) should not be co-claimed with the POCPS procedure. The diagnostic application was placed under category 5 – diagnostic imaging services, but it should be under category 3 – therapeutic procedures (subject to the multiple operation rule).

ESC noted the proposed MBS fees were 2.3 times that of ERCP alone for the therapeutic application and 1.6 times that of ERCP alone for the investigative application. ESC noted concerns raised in the policy paper that there was not sufficient justification of the proposed fees for the services, including duration and detailed information about the complexity of the procedure to inform an implementation process for the services. ESC noted that two references were included (Alberta Health Service reimbursement and Sandha et al. 2018<sup>2</sup>) that do not provide sufficient rationale or were unavailable for corroboration. ESC considered reimbursement in Canada may not be applicable to the MBS. The pre-ESC response included the American Society for Gastrointestinal Endoscopy (ASGE) ERCP complexity table. The applicant suggested that the complexity for the service is in line with grade 4 (intraductal image guided therapy). However, ESC noted that Grade 3 included biliary stone extraction and biliary stricture

<sup>2</sup> Sandha J, van Zanten, SV, Sandha G (2018). The safety and efficacy of single-operator cholangioscopy in the treatment of difficult common bile duct stones after failed conventional ERCP. *J Can Assoc Gastroenterol*, 1(4):181-190.

procedures. In addition, ESC noted that ERCP procedures have a single fee although individual procedures vary in complexity. ESC considered this evidence was not sufficient to suggest that POCPS was more complex, or took longer time, than ERCP.

The item descriptors only included a 75% rebate, consistent with an in-hospital procedure. ESC advised that the proposed service would be used as an in-hospital procedure and outpatient procedure. ESC noted that currently around 15% of the billed ERCP procedures are outpatient procedures.

ESC noted that the initial capital costs were over \$redacted<sup>3</sup> for the Spyglass Digital Controller with further costs for the Autholith Generator used for the therapeutic indication. ESC noted that the cost of consumables was \$redacted for the therapeutic indication and \$redacted for the diagnostic indication. ESC also noted that a large amount of these costs was due to a disposable catheter estimated to cost \$redacted. ESC noted that there were differences in the capital and consumable equipment outlined in the ADAR, the SpyGlass Brochure, and the American Society for Gastrointestinal Endoscopy (ASGE) Technology Committee's 2016 Status Evaluation Report on cholangiopancreatography (Table 4). ESC noted the ASGE reported costs of approximately \$80,000 equipment (\$56,402 United States dollars) which did not include the Digital Controller or Autolith Generator. ESC noted that there were updates to the technology in 2018 which could account for the differences. ESC requested the applicant address the differences in its pre-MSAC response.

The ADAR proposed the costs of POCPS consumables will be reimbursed by private health insurance as a part of the POCPS hospitalisation, however ESC was unaware of private hospitals currently performing POCPS. Currently in Australia POCPS is performed at a small number of public hospitals and it is unclear whether private hospitals would consider offering POCPS given costs and small numbers of estimated procedures. ESC noted that there was no clear funding mechanism for these costs, and there may be potentially high out-of-pocket costs for patients as the bulk billing rate for ERCP is low (16.8%).

ESC noted that public consultation feedback from the Gastroenterological Society of Australia (GESA) was positive, supporting POCPS as superior for the removal of difficult biliary stones. GESA claimed POCPS offers better visualisation and accurate targeting of biliary stones, as well as earlier diagnosis. However, ESC noted that there was no data to support the claim that time to diagnosis was faster. ESC noted that the Pancare Foundation also supported this application, claiming that POCPS was better for patients than repeat procedures of ERCP, and may allow earlier detection of biliary cancers. The Pancare Foundation and Cancer Council Australia also claimed that POCPS reduced the risk of cancer progressing to a late stage. ESC noted that a consumer was concerned about the lack of good evidence on safety, effectiveness and adverse events.

ESC noted that there is no estimate of the likely out of pocket costs consumers would incur. ESC considered that POCPS would be provided in major hospitals and consumers in regional areas would have to travel to have the procedure. ESC considered that there would be benefits to patients having POCPS performed by experienced practitioners as practitioner skill could affect procedural success.

ESC noted that the therapeutic indication included direct evidence from two clinical trials: an RCT of POCPS versus ERCP (Angsuwatcharakon et al. 2019)<sup>4</sup>, and an RCT of POCPS vs laparoscopic

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<sup>3</sup> The cost was corrected to \$redacted in the applicant's pre-MSAC response.

<sup>4</sup> Angsuwatcharakon P, Kulpacharapong S, Ridditid W, Boonmee C, Piyachaturawat P, Kongkam P et al. (2019). Digital cholangioscopy-guided laser versus mechanical lithotripsy for large bile duct stone removal after failed papillary large-balloon dilation: a randomized study. *Endoscopy*, **51**(11):1066-1073.

choledochotomy (Li et al. 2021).<sup>5</sup> ESC noted that only two sources of evidence presented for the diagnostic indication were relevant: a randomised controlled trial (RCT) (Gerges et al. 2020)<sup>6</sup>, which informed most of the evidence for diagnostic efficacy, and a cohort study (Draganov et al. 2012).<sup>7</sup>

ESC noted that the evidence did not always include patients who had first-line ERCP which is the proposed population for the PICO. ESC noted from the commentary that for both indications, further supportive evidence in the form of naïve indirect comparisons was referenced in the ADAR but not evaluated. ESC agreed with the commentary that there were methodological deficiencies with the indirect comparison approach in the ADAR. ESC acknowledged the pre-ESC response that the inclusion of a comparator within the search strategy would not overly restrict the results and considered this may be reasonable. ESC noted that the applicant stated that the risk of bias assessment may not be as relevant as it should have already been done during the peer review process, but ESC did not agree that this was either common practice or a reason to not provide an in-depth risk of bias assessment.

ESC considered it appropriate to focus solely on the comparative evidence. However, regarding comparative safety, ESC noted that the studies had small samples and no systematic capture of adverse events, so considered it likely that they were inadequate to capture accurate adverse event rates. ESC considered safety data from larger non-comparative studies should supplement the direct comparative evidence but this was not available from the ADAR.

For the investigative indication, ESC noted that the RCT by Gerges et al. (2020) reported no significant difference in the rate of pancreatitis between the two treatment arms. For the therapeutic indication, ESC noted that adverse events were not explicitly recorded. The study by Angsuwatcharakon et al. (2019) reported one patient in each treatment arm with pancreatitis (6% of patients in each arm), but the sample size was very small (n=16 per arm). The study by Li et al. (2021) reported patients with pancreatitis and bleeding. The absolute difference in adverse events for both studies was small. ESC considered there are well characterised adverse events associated with POCPS (e.g. pancreatitis and cholangitis). ESC considered that further evidence (possibly in the form of indirect studies using absolute rates) was needed. There was uncertainty in how adverse events differ for POCPS and ERCP. ESC also considered that rarer side effects may not be captured in the provided studies.

Regarding comparative effectiveness for the diagnostic application, ESC considered there to be several issues with the RCT (Gerges et al. 2020). The study population did not have prior ERCP and was not applicable to the proposed MBS populations. The proportion of patients diagnosed with malignancy was not equal in the arms, and ESC considered this could be due to unequal randomisation. Verification bias may be present due to patients undergoing different interventions to confirm malignancy. The results reported a significant difference in sensitivity, but the estimate is at risk of bias. Additionally, the study had a small number of participants (n=60) and there was no difference in the number of procedures needed to reach diagnosis.

ESC noted that the study by Draganov et al. (2012) included 26 patients (17 with cancer, 9 without) who had prior ERCP. The tests used included ERCP-guided brushings, ERCP-guided biopsies and POCPS-guided biopsies. ESC considered there to be several issues with this cohort study. ESC noted that it was unclear if the pathologists knew the results of the ERCP-guided

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<sup>5</sup> Li G, Pang Q, Zhai H, Zhang X, Dong Y, Li J et al. (2021). SpyGlass-guided laser lithotripsy versus laparoscopic common bile duct exploration for large common bile duct stones: a non-inferiority trial. *Surg Endosc*, **35**(7):3723-3731.

<sup>6</sup> Gerges C, Beyna T, Tang RSY, Bahin F, Lau JYW, van Geenen E et al. (2020). Digital single-operator peroral cholangioscopy-guided biopsy sampling versus ERCP-guided brushing for indeterminate biliary strictures: a prospective, randomized, multicenter trial (with video). *Gastrointest Endosc*, **91**(5):1105-1113.

<sup>7</sup> Draganov PV, Lin T, Chauhan S, Wagh MS, Hou W, Forsmark CE (2011). Prospective evaluation of the clinical utility of ERCP-guided cholangiopancreatography with a new direct visualization system. *Gastrointest Endosc*, **73**(5):971-979.

brushings and biopsies before reading the results of the POCPS-guided biopsies, which would have improved the sensitivity of the test. ESC noted the reference standard (surgery), which was applied variably, follow-up and other testing, but the type of 'other testing' was not disclosed.

Overall, ESC considered there to be issues with applicability, a lack of randomisation and a differing reference standard. ESC considered the estimate of effect, which had high sensitivity, to be uncertain. ESC noted that the ADAR reported the risk of bias as low however, ESC considered the risk of bias is more likely to be high, particularly concerning selection bias, variable reference standard and lack of blinding.

For the diagnostic indication, a linked evidence approach to the clinical claim was used. The pre-ESC response provided further rationale that POCPS produces fewer inconclusive results, resulting in a reduction in repeated diagnostic procedures and unnecessary surgical resection of benign strictures.

ESC noted that the change in clinical management data was presented, but had concerns with:

- applicability (as they were overseas data and the populations had different malignancy rates)
- applicability in the Australian context of clinical decision-making
- bias, which was not adequately assessed
- the reduction in further procedures not being supported (the study by Gerges et al. (2020) reported no difference but did not provide numbers).

For the therapeutic application, ESC considered the risk of bias for the Angsuwatcharakon et al. (2019) to be high (not low) due to incomplete results and selective reporting domains. ESC considered the study may not be fully generalisable to the Australian context as it included patients with common bile duct stones only while POCPS is promoted for more difficult biliary stones. ESC considered that there is potential for bias where practitioners may prefer laser lithotripsy and chosen this in the study if allocation concealment was not adequate. In Angsuwatcharakon et al. (2019), three of six patients who did not have complete stone clearance with ERCP-ML had stone clearance after switching to laser lithotripsy in the same session. Other issues ESC identified included were the small sample size(n=32) for the primary effectiveness outcome of complete stone clearance and the confidence interval for the relative effectiveness being wide.

In comparison, ESC noted that the Li et al. (2021) study was methodologically stronger, but the estimate for relative effectiveness was not statistically significant.

ESC noted that the clinical claim of superior effectiveness was assumed for both the therapeutic and investigative indications. ESC noted that the commentary suggested revising the clinical claim of superior effectiveness over ERCP-guided lithotripsy to non-inferior effectiveness. ESC considered this to be very conservative, and that there was likely enough evidence to support the claim of superior effectiveness. ESC agreed with the commentary that the claim of superior effectiveness compared to laparoscopic choledochotomy for the therapeutic indication was not supported, and that this should be revised to non-inferior effectiveness. This was accepted by the pre-ESC response.

For the economic evaluation, ESC noted that a cost-effectiveness analysis was performed for both the diagnostic and therapeutic indications. ESC considered this appropriate. ESC considered a cost-utility analysis would not have changed the conclusion.

ESC noted the economic evaluation did not include adverse events. This implicitly assumed POCPS has non-inferior safety compared with ERCP and laparoscopic choledochotomy however, ESC considered non-inferior safety compared to ERCP was not established. Similarly, the

economic model did not capture adverse events from pancreaticoduodenectomy for suspected malignancy in the investigative indication.

For the diagnostic indication, ESC considered there was uncertainty in the modelled inputs for sensitivity and specificity of the intervention and comparator due to uncertainties in the clinical evidence. ESC considered sensitivity analysis of these inputs would be useful for MSAC. ESC noted that the base case resulted in a \$6,808 cost per correctly diagnosed patients. The incremental cost-effectiveness ratio (ICER) was dominant when including the cost of unnecessary surgery for patients with benign conditions (not cancer) and the cost of unnecessary treatment for patients with incorrect diagnoses were included. ESC considered a further sensitivity analysis using the same MBS cost for POCPS and ERCP also resulted in dominant ICERs. This had a small impact on the ICER. ESC considered that POCPS appears to be a cost-effective alternative to ERCP and ERCP with laparoscopic choledochotomy, under all different clinical claim scenarios.

For the therapeutic indication, ESC noted that a weighted comparator of repeat ERCP-guided lithotripsy (63%) and laparoscopic choledochotomy (27%) was used. ESC considered an analysis where the comparator was ERCP only (laparoscopic choledochotomy used third line) would be informative as POCPS may replace laparoscopic choledochotomy in the second line setting. This resulted in a dominant ICER. ESC considered the assumption that POCPS has 83% stone clearance compared with 96% for laparoscopic choledochotomy was not consistent with the assumption of non-inferiority. ESC noted assuming non-inferiority (83% stone clearance) with for laparoscopic choledochotomy resulted in a dominant ICER. Further sensitivity analyses using the same MBS fee for POCPS and ERCP also resulted in dominant ICERs.

ESC noted the net cost to the MBS of POCPS was small – less than \$50,000 per year for the therapeutic application and less than \$5,000 per year for the investigative application. This was due to POCPS replacing ERCP and laparoscopic choledochotomy (therapeutic only).

ESC noted that for the therapeutic indication, the utilisation estimates and financial impacts were based on a mixed-market share and epidemiological approach. This was done using Medicare statistics for ERCP procedures, expert opinion (2021 Advisory Board) and internal data from the applicants. ESC considered the market share assumptions to be uncertain. ESC noted that the ADAR assumed POCPS would account for 20-77% of ERCP procedures for difficult biliary stones, and 10-39% of laparoscopic choledochotomy. ESC considered it would be useful to test different growth rates in ERCP and laparoscopic choledochotomy separately (POCPS is superior to one and non-inferior/inferior to the other). This resulted in modest changes in net cost to the MBS. ESC considered that uptake from ERCP and laparoscopic choledochotomy may differ. Reducing the MBS fee for POCPS to be the same as ERCP resulted in net savings to the MBS.

For the diagnostic indication, the ADAR estimated that POCPS would substitute for 13-51% of ERCP procedures for indeterminate biliary strictures. ESC considered there to be uncertainty in the market share assumptions. ESC requested further sensitivity analysis reducing the MBS fee for POCPS to be the same as ERCP. This resulted in net savings to the MBS.

## **17. Applicant comments on MSAC's Public Summary Document**

The Applicant is pleased with the decision by the MSAC to recommend listing of POCPS for patients with indeterminate biliary strictures and difficult biliary stones to facilitate equitable access to the gold standard of care. The Applicant also welcomes the recognition of the primary sclerosing cholangitis (PSC) as a high clinical need population to be served by this technology.

The Applicant notes that the MSAC-proposed fee for therapeutic POCPS may not reflect the time required and technical complexity of the procedure. The Applicant encourages further engagement with Australian clinicians (including the nominated clinicians) and/or representative

bodies (GESA) to identify the appropriate fee for therapeutic POCPS relative to other comparable services listed on the MBS.

## **18. Further information on MSAC**

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