

# Cellvizio confocal endomicroscopy system for characterising pancreatic cysts

Medtech innovation briefing

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## Summary

Cellvizio is a confocal laser endomicroscopy (CLE) system with a fibre-optic probe for real-time imaging of tissues. It is designed for use as an adjunct to the standard endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) procedure, to characterise pancreatic cysts and provide additional information to help guide therapeutic decisions. The evidence summarised in this briefing comes from 2 feasibility and 3 pilot studies with a total of 138 adult patients. The diagnostic accuracy for Cellvizio was reported to be between 71% and 87% in 3 studies compared with histopathology, EUS-FNA or a committee consensus. In 2 studies, images were successfully obtained in all patients. In another study, images were successfully obtained in most (17 of 18) patients. The device was used to identify and validate new diagnostic criteria for pancreatic cyst types in 4 studies. The numbers of safety incidents in 2 Cellvizio studies were higher than reported in a previous EUS-FNA-only study. The main capital component of the Cellvizio system costs £79,000 with installation, commissioning and initial training costs of £2,145. Each fibre-optic miniprobe (AQ-Flex 19) can be used up to 10 times and costs £4,000. All costs are excluding VAT.

<p><b>Product summary and likely place in therapy</b></p> <ul style="list-style-type: none"> <li>• Cellvizio is a CLE system with a fibre-optic miniprobe. The system allows imaging of tissues by generating 'optical biopsies', that is, real-time microscopic images of tissue, taken during an endoscopic procedure. These images can be used as well as or instead of information obtained by standard biopsies.</li> <li>• The Cellvizio CLE system (see model details below) is designed for use as an adjunct to the standard EUS-FNA procedure for the characterisation of pancreatic cysts.</li> </ul>	<p><b>Effectiveness and safety</b></p> <ul style="list-style-type: none"> <li>• Five studies are included in this briefing. Of these, 2 were feasibility studies, and 3 were pilot studies. The studies involved a total of 138 adult patients.</li> <li>• In 1 prospective, single-arm feasibility and safety study, images were obtained in 17 of 18 people enrolled. Two people (11%) developed pancreatitis.</li> <li>• One prospective, single-arm feasibility study (n=30) found that Cellvizio had a diagnostic accuracy of 87% for detecting potentially malignant pancreatic cysts compared with histopathology or a committee consensus.</li> <li>• One prospective, single-arm pilot study (n=57) suggested that epithelial villous structures visualised using Cellvizio were strongly associated with potentially malignant cysts. Cellvizio identified these cysts with a diagnostic accuracy of 71% compared with histopathology or a committee consensus.</li> <li>• One prospective, single-arm pilot study in 31 patients demonstrated that Cellvizio could identify benign cysts with an accuracy of 87% compared with histopathology, EUS-FNA or a committee consensus.</li> <li>• A retrospective analysis of a prospective single-arm pilot study (n=33) identified and validated new diagnostic criteria for benign or potentially malignant cysts using Cellvizio.</li> </ul>
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Technical and patient factors	Cost and resource use
<ul style="list-style-type: none"> <li>• The focus of this briefing is the Cellvizio 100 Series F400-v2 Laser Scanning Unit (LSU) operating at a wavelength of 488 nm in combination with the AQ-Flex 19 Confocal Miniprobe. Other Cellvizio models used in research are not considered.</li> <li>• The AQ-Flex 19 is loaded into a 19-gauge EUS needle and attached by a locking device. This is then passed through the accessory channel of a standard endoscope.</li> <li>• Fluorescein dye is used to enhance image contrast.</li> <li>• The system is intended for use in secondary or tertiary care units that have the relevant equipment as well as appropriate expertise and experience of performing EUS-FNA. The intended users are endoscopists trained in the EUS-FNA procedure.</li> <li>• The Cellvizio system can also be used for other clinical applications, each requiring the use of a different type of miniprobe. Other miniprobes and clinical applications are outside the scope of this briefing.</li> </ul>	<ul style="list-style-type: none"> <li>• The main capital components of the Cellvizio system cost £79,000.</li> <li>• Installation, in-servicing and initial training cost £2,145. The optional digital imaging and communications in medicine (DICOM) connectivity module costs £2,730.</li> <li>• Each AQ-Flex 19 costs £4,000. Each miniprobe can be used for up to 10 procedures in multiple patients.</li> <li>• All costs stated are excluding VAT.</li> <li>• No published evidence on cost consequences and resource use was available.</li> </ul>

## Introduction

Pancreatic cysts are fluid-filled sacs on or in the pancreas. There are different types of pancreatic cysts which vary in their potential for malignancy and the type of treatment needed. Typically, benign cysts include pseudocysts and serous cystadenomas. Potentially malignant cysts include intraductal papillary mucinous neoplasms and mucinous cystadenomas. Other abnormalities, such as neuroendocrine neoplasms, may look like cysts and need to be correctly identified before a diagnosis can be made. Most pancreatic cysts are benign.

No data are available for the UK, but the reported prevalence of pancreatic cysts in the general population (derived from studies done in the US, Japan, Holland and Ireland) varies from 1.2% to 24.3% (de Jong et al. 2012). Most pancreatic cysts do not cause symptoms and are detected by chance when people have abdominal MRI or CT scans. According to the American Gastroenterological Association, unsuspected pancreatic cysts are found in about 15% of patients having an abdominal MRI for other indications (Vege et al. 2015).

Endoscopic ultrasound with fine needle aspiration (EUS-FNA) is the standard procedure used to characterise pancreatic cysts. In the procedure, the person is sedated and an endoscope with an ultrasound probe is passed through the mouth and stomach into the duodenum. Ultrasound waves are used to identify abnormalities within the pancreas. If an abnormal area is detected, a very fine needle can be passed into it to take a sample of tissue or fluid. EUS-FNA alone may not be accurate enough to characterise all pancreatic cysts and the analysis of cyst fluid does not consistently allow specific cyst types to be identified or predict malignancy potential. An inconclusive EUS-FNA typically results in a follow-up EUS-FNA or CT-guided FNA procedure, with surgery being considered for some people if there is concern about the nature of the lesion. Providing a more accurate diagnosis during the EUS-FNA procedure would inform more appropriate management, including options for surgery and surveillance intervals. Needle-based confocal laser endomicroscopy (nCLE) generates 'optical biopsies', providing endoscopists with real-time microscopic images of tissues to use in addition to or in place of information obtained by standard biopsies. This could potentially allow for a quicker, more accurate diagnosis of benign and malignant cysts.

## Technology overview

This briefing describes the regulated use of the technology for the indication specified, in the setting described, and with any other specific equipment referred to. It is the responsibility of healthcare professionals to check the regulatory status of any intended use of the technology in other indications and settings.

### *About the technology*

#### CE marking

Mauna Kea Technologies received CE marking for the Cellvizio 100 Series F400-v2 Laser Scanning Unit (LSU; wavelength 488 nm) system (from here onwards referred to as 'Cellvizio system') in April 2011 and for the AQ-Flex 19 Confocal Miniprobe (from here onwards referred to as the

AQ-Flex 19) in September 2011. In Europe, the Cellvizio system with AQ-Flex 19 is regulated as a class IIa medical device (within the scope of Directive 2007/47/EC).

The AQ-Flex 19 is designed to be advanced through an endoscopic ultrasound (EUS) needle and, combined with the 488 nm excitation wavelength of the Cellvizio system, is used specifically for the characterisation of pancreatic cysts.

## Description

The Cellvizio system is a probe-based confocal laser endomicroscopy (CLE) system. When combined with the AQ-Flex 19, the system allows CLE imaging of tissues through an endoscopic needle, a technique also known as needle-based CLE (nCLE). Using this method, the technology generates 'optical biopsies', providing endoscopists with real-time microscopic video images of tissues.

The Cellvizio system is composed of several components which are integrated into a cart. These are:

- Main components:
  - Laser scanning unit (LSU; F400-v2; 488 nm laser source). This is a software-operated device classified as a class 2M laser product. The LSU includes a Class IIIB laser source that produces continuous laser emission at 488 nm, a laser scanning module (to expand and deflect the laser beam), lenses (used to focus the light at the tissue area of interest and refocus reflected light onto the detector) and a detector (to collect the photons corresponding to the illumination of 1 given fibre at a time). Data acquired by the detector are transmitted to the processor.
  - AQ-Flex 19. This carries the laser beam to the tissue and captures the light emitted back. It contains 10,000 optical fibres, and has a diameter of 0.85 mm with a length of 4 m. The AQ-Flex 19 is compatible with a 19-gauge endoscopic needle. Its imaging depth ranges from 40 to 70 micrometres and depth of focus is 30 micrometres. It has a maximal field of view of 325 micrometres, and a lateral resolution of 3.5 micrometres (at 1,000 times magnification). The AQ-Flex 19 can be sterilised and reused for up to 10 examinations in multiple patients, but the locking devices used to secure its position inside the endoscopic needle are single-use only.
  - Confocal processor with Cellvizio software. This is a computer used to record and store images and video sequences. Cellvizio software 2.2 has a digital imaging and

communications in medicine (DICOM) connection option, which is compatible with standard NHS systems for the export of images and reports. It includes the Endomicroscopy Virtual Assistant software, which provides reference videos to assist during procedures, identifies visually stable segments of videos and prepares images for printing.

- Peripherals (included):
  - keyboard
  - pointing device (trackball)
  - footswitch (to start and stop the laser emission and imaging). A separate button switches the LSU on and off
  - screen
  - video converter
  - isolation transformer
  - printer.
- Peripherals (optional):
  - sterilisation tray
  - external hard drive (for data transfer).
- Accessories: These include the single-use confocal miniprobe locking device, Cletop-S confocal miniprobe connector cleaning system, storage box, protective caps (intended to protect the connector of the AQ-Flex 19 during sterilisation), spare fuses and user documentation.

Before the EUS with fine needle aspiration (FNA) procedure, the AQ-Flex 19 is loaded into a standard 19-gauge needle. The position of the AQ-Flex 19 is secured using the locking device that attaches the probe to the inlet of the needle biopsy channel of the endoscope. Fluorescein dye (2.5 to 10 ml of 10% fluorescein sodium) is injected intravenously immediately before nCLE imaging and is taken up by the cells of the cyst wall. During EUS examination of the pancreas, cysts needing further investigation are identified. The preloaded needle is then used to puncture the target cyst and the tip of the AQ-Flex 19 is moved through the needle and into the cyst, under EUS guidance, until the probe touches the cyst wall. The laser beam is then shone through the AQ-Flex 19, onto the cyst wall to activate the fluorescein. The photons emitted are reflected back to the AQ-Flex 19 and deflected to an ultra-sensitive detector. Software in the LSU reconstructs

the image from the detector signal and passes it to the Cellvizio processor, which then projects the image as a 12-frame per second video display. Images show details of the pancreas including vessels, cells, connective tissue and cysts. Real-time images of the tissue (which can be recorded and saved) are displayed on the screen to aid diagnosis. The average duration of an nCLE procedure is 7 minutes. The AQ-Flex 19 is removed and a syringe is attached to the proximal end of the needle for cyst aspiration.

The Cellvizio system can also be used in other medical specialties including gastroenterology, pulmonology, and urology. Different indications need different types of confocal miniprobes and are outside the scope of this briefing.

## Setting and intended use

The Cellvizio system is intended to be used with the AQ-Flex 19 for confocal laser imaging of pancreatic cysts during a standard EUS-FNA procedure.

The Cellvizio system is intended for use in secondary care by endoscopists who have been trained to use the system. Training is given by the manufacturer through onsite training courses and online resources. Except for allergy to fluorescein, there are no known contraindications associated with use of the Cellvizio system, as long as it is used according to the instructions provided by the manufacturer.

## Current NHS options

There is currently no NICE guidance for pancreatic cysts and no definitive consensus on their management.

The NICE guideline on [recognition and referral for suspected cancer](#) recommends the referral of people for pancreatic cancer (for an appointment within 2 weeks) if they are aged 40 and over and have jaundice.

The guideline also recommends an urgent direct access CT scan within 2 weeks of referral (or an urgent ultrasound scan if CT is not available) to assess people aged 60 and over for pancreatic cancer if they have weight loss and any of the following symptoms:

- diarrhoea
- back pain

- abdominal pain
- nausea
- vomiting
- constipation
- new-onset diabetes.

Abdominal CT or MRI scanning may indicate the presence of pancreatic cysts, whether carried out to investigate associated symptoms or for other indications. After a cyst is identified, further tests (EUS-FNA as standard or CT-guided FNA) are done to classify the cyst as benign or malignant. The results of these tests help to determine whether any follow-up is needed (such as surgery or surveillance). Decisions are based on the risk of malignancy, and the presence and severity of any cyst-related symptoms. Provided the patient is deemed fit, surgery is considered the most appropriate treatment option if the cyst is confirmed as malignant.

NICE is aware of the following CE-marked devices that appear to fulfil a similar function to the Cellvizio system:

- SpyGlass (Boston Scientific); NICE has produced a medtech innovation briefing on the [SpyGlass direct visualisation system for diagnostic and therapeutic procedures during endoscopy of the biliary system.](#)

## *Costs and use of the technology*

Information on the price of the technology was provided by the manufacturer and has been converted from euros to GBP (at 1 euro to 0.78 GBP). All prices exclude VAT:

- Cellvizio 100 series system: £79,000.
- Installation, commissioning and initial training: £2,145.
- Each AQ-Flex 19 can be used up to 10 times and costs £4,000. After each use, the manufacturer recommends that the probes are sterilised with an enzyme detergent using a low temperature sterilisation system.
- The optional DICOM connectivity module costs: £2,730.

According to the manufacturer, the technology has a lifespan of at least 10 years if routinely maintained by the end user. A survey reported by Meenan et al. (2011) suggests that around



85 EUS-FNA procedures are done annually at each suitably equipped centre in the UK. Many of these procedures will be to investigate pancreatic cysts and given that the Cellvizio system is used during the EUS-FNA procedure, this figure represents an estimate of potential annual Cellvizio usage. Using an annuity calculation and assuming a technology lifespan of 15 years with a discount rate of 3.5%, an estimate of (technology only) cost per procedure is £486. This includes the cost of the DICOM connectivity module. This does not include the cost of EUS-FNA, NHS staff time, facility or capital costs.

The comparator treatment is EUS-FNA alone. NHS reference costs list the average unit cost of 'Diagnostic Endoscopic Upper Gastrointestinal Tract Procedures with Biopsy, 19 years and over' as £469 (Department of Health 2015; code FZ61Z). In addition, Sharples et al. (2012) provides relevant cost and price information from the finance department of Papworth Hospital. This allows a calculation for the estimated unit cost of EUS-FNA that is not as nationally representative as NHS reference costs but may be more precise. The calculation is inclusive of the following costed NHS resource use: annuitised, fixed and per treatment consumable clinical costs (EUS scope, ultrasound processor, aspiration needle etc.), consultant and nurse costs, hospital overheads and capital costs. This estimate gives an (inflation adjusted) unit cost of £932. Assuming a similar level of NHS labour time use, the unit cost of EUS-FNA with Cellvizio is about £1,418 (£932+£486).

No other practical difficulties have been identified in using or adopting the technology.

### *Likely place in therapy*

The Cellvizio system is designed to be used as an adjunct to the standard EUS-FNA procedure for diagnosing and managing indeterminate pancreatic cysts.

### *Specialist commentator comments*

One specialist commentator stated that Cellvizio should not be considered less invasive than an EUS-FNA procedure because the Cellvizio procedure also involves puncturing the cyst. The same commentator suggested that the time the probe has contact with the pancreatic tissue in the Cellvizio procedure may be longer than with EUS-FNA, because the time taken to image may be longer than the time taken to aspirate fluid.

One specialist commentator suggested that EUS-FNA alone is not accurate enough to characterise all pancreatic cysts. Another specialist commentator suggested that the available evidence on the development of Cellvizio diagnostic criteria, especially for mucinous pancreatic cysts, is still limited and highlighted the need for more research to address this knowledge gap.

One specialist commentator mentioned that because intravenous administration of fluorescein is part of the nCLE process, allergy to fluorescein dye should be listed as a contraindication.

## *Equality considerations*

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. In producing guidance, NICE aims to comply fully with all legal obligations to:

- Promote race and disability equality and equality of opportunity between men and women.
- Eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

The prevalence of pancreatic cysts increases with age, which is a protected characteristic defined in the Equality Act 2010. Up to 90% of people with von Hippel-Lindau syndrome, a rare genetic disorder affecting around 1 in 36,000 people, develop serous cystadenoma (Jana et al. 2015).

## **Evidence review**

### *Clinical and technical evidence*

#### **Regulatory bodies**

A search of the Medicines and Healthcare Products Regulatory Agency website revealed no manufacturer Field Safety Notices or Medical Device Alerts for this device. No reports of adverse events were identified from a search of the US Food and Drug Administration (FDA) database: Manufacturer and User Device Facility Experience (MAUDE).

#### **Clinical evidence**

Of the 27 relevant publications identified, 22 were excluded because they were abstracts. Consequently, 5 studies are included in this briefing. Of these, 2 were feasibility studies, and 3 were pilot studies. A total of 138 people were included in the studies. Two of the pilot studies include largely overlapping cohorts, with different outcomes.

## ***Pilot studies***

Konda et al. (2013; [table 2](#)) carried out a multinational, multicentre, prospective pilot study. The aims of the study were to assess the diagnostic accuracy of Cellvizio to differentiate benign and potentially malignant cysts, and the safety of the technique. A total of 57 people scheduled for endoscopic ultrasound with fine-needle aspiration (EUS-FNA) had needle-based confocal laser endomicroscopy (nCLE) imaging. The final diagnosis was either based on histopathological diagnosis of specimens from people who had had surgery (n=14), or by clinical diagnosis after a blinded committee consensus review of images by 5 investigators (n=43). Results from surgical and non-surgical patients (n=26) were analysed to provide definitions for images associated with various pancreatic structures. In the remaining 31 patients, a blinded committee consensus review of the nCLE images suggested that the presence of epithelial villous structures was associated with potentially malignant cysts (p=0.004) and provided diagnostic accuracy of 71%, sensitivity of 59%, specificity of 100%, positive predictive value (PPV) of 100%, and negative predictive value (NPV) of 50%. The overall complication rate was 9% and included pancreatitis (1 mild case, 1 moderate case), transient abdominal pain (n=1), and intracystic bleeding not needing any further measures (n=3).

Napoleon et al. (2015a; [table 4](#)) carried out a prospective multicentre pilot study to identify and validate new diagnostic criteria for nCLE of pancreatic cysts. A total of 31 people admitted for EUS-FNA for pancreatic cysts had nCLE. Final diagnosis was based on histopathology in patients who had had surgery (n=7), or on conclusive FNA results (n=11). For the remaining patients (n=13), 6 investigators and 2 pathologists reviewed all available information to make a final diagnosis by committee consensus. A superficial vascular network pattern visualised on nCLE was identified as the significant diagnostic criterion for benign cysts by non-blinded consensus review by 6 investigators. The overall diagnostic accuracy, sensitivity, specificity, PPV, and NPV for diagnosing benign cysts were 87%, 69%, 100%, 100% and 82% respectively. Interobserver agreement was substantial (kappa=0.77). A single event of mild acute pancreatitis was recorded, resulting in an overall complication rate of 3.2%.

Napoleon et al. (2015b; [table 5](#)) carried out a retrospective analysis of prospectively collected data (from largely the same patients described in Napoleon et al. 2015a) to determine new nCLE diagnostic criteria to characterise pancreatic cysts and to validate the performance of these criteria (n=33). The final diagnosis was based on histopathological diagnosis of specimens from people who had had surgery (n=20). A committee consensus review of all information produced the final diagnosis in those who had not had surgery (n=13). New nCLE criteria were identified for various cyst types (mucinous cystic neoplasms [MCN], pseudocysts [PC] and cystic neuroendocrine neoplasms [NEN]). People with cystic NEN were excluded from the subsequent validation of the identified criteria due to the small number (n=2). nCLE yielded a conclusive diagnostic result in 74%

(n=23) of 31 surgical and non-surgical participants. Of these, 87% (n=20) were correct and 13% (n=3) were incorrect when compared with final diagnosis. Interobserver agreement for cyst types ranged from 0.35 for potentially malignant cysts (indicating fair agreement) to 1.00 for benign cysts (indicating perfect agreement). The overall agreement for all cysts was kappa=0.72 (indicating substantial agreement).

### ***Feasibility studies***

A US-based single-centre, prospective study was carried out by Konda et al. (2011; [table 1](#)) to evaluate the feasibility of using the Cellvizio system in 18 people having EUS-FNA for the evaluation of pancreatic cysts. Images were obtained in 17 of 18 people, but technical challenges were encountered in 6 of 18 attempts to image. There were no device malfunctions. Good to very good quality images were obtained in 10 of the 17 people. Image quality was rated as moderate in 5 people, and low or poor in 2 people. Two serious adverse events occurred; both were pancreatitis requiring hospitalisation.

In a single-centre, prospective, single-arm feasibility study performed in the US, Nakai et al. (2015; [table 3](#)) investigated the feasibility, safety, and diagnostic accuracy of cystoscopy and nCLE in the clinical diagnosis of potentially malignant cysts. Thirty people having EUS-FNA for the evaluation of pancreatic cysts were examined using 3 sequential EUS-guided procedures: nCLE with the Cellvizio system, followed by cystoscopy with the SpyGlass system, and then FNA. In people who had had surgery (n=2), the final diagnosis was based on histopathology. In people who had not had surgery (n=28), diagnosis was established by 2 independent, blinded investigators based on clinical presentation, combined with image findings on EUS, CT, and MRI, as well as fluid analysis and cytology on EUS. Image quality was reviewed by 1 non-blinded investigator. The procedure was technically successful except for 1 probe exchange failure. Image acquisition was 100% successful, with 90% of the nCLE images and 67% of the cystoscopy images rated as excellent quality. In all patients, diagnostic accuracy for nCLE in potentially malignant cysts was 87%, sensitivity was 77%, and specificity was 100%. In high certainty cases (n=18), the diagnostic accuracy of nCLE for potentially malignant cysts was 89%, sensitivity was 80%, and specificity was 100%. Pancreatitis developed in 2 people after the procedures. The procedures were carried out sequentially, so it is unclear which (if any) caused the complications.

### **Recent and ongoing studies**

Seven ongoing or in-development trials on Cellvizio for pancreatic cysts were identified in the preparation of this briefing.

NCT01563133: a French interventional study designed to measure the diagnostic accuracy of Cellvizio in the characterisation of pancreatic cysts, lymph nodes near the gastrointestinal tract and pancreatic masses. This is an ongoing study with a study completion date of June 2017 (last updated April 2016).

NCT01770405: a US-based, prospective, observational study to assess the diagnostic performance of Cellvizio in diagnosing masses and cystic tumours of the pancreas, lymph nodes and submucosal lesions of the GI tract. This is an ongoing study with an estimated study completion date of September 2016.

NCT02523170: a UK-based, interventional study to determine the safety and efficacy of Cellvizio in patients with suspected cystic tumours of the pancreas. This is an ongoing study with an estimated study completion date of July 2017.

NCT02494388: a multinational, prospective, observational study to determine the diagnostic accuracy of Cellvizio in a cohort of patients with cystic pancreatic tumours. This is an ongoing study with an estimated study completion date of June 2017.

NCT01734967: a multinational, prospective, interventional study aiming to describe confocal imaging criteria for pancreatic masses, lymph nodes or liver metastases identified during EUS procedures for pancreatic cancer staging. It will also evaluate the feasibility and safety of examination using Cellvizio. This is an ongoing study with an estimated study completion date of December 2017.

NCT02516488: a US-based, prospective, observational study to assess the accuracy of Cellvizio for diagnosing cystic pancreatic lesions. This is an ongoing study with an estimated study completion date of November 2016.

TCTR20140402001: a Thai prospective, observational study to investigate the efficacy of Cellvizio for differentiating solid pancreatic masses. Recruitment was completed in February 2014.

### *Costs and resource consequences*

There are no available data relating to the prevalence of pancreatic cysts in the UK population. There are more than 9,000 newly diagnosed cases of pancreatic cancer in the UK each year, with an incidence rate of around 14 per 100,000 people (Cancer Research UK 2016). It is estimated that 7,000 to 14,000 EUS procedures are needed in the UK each year for the diagnosing, assessing and staging likely pancreatobiliary cancers (Meenan et al. 2011). EUS is also available at 65 centres in

the UK, with an average of 85 EUS-FNA procedures done annually at each unit (Meenan et al. 2011). Cellvizio is designed to be used as an adjunct to EUS-FNA and so this can provide some indication of potential NHS usage.

According to the manufacturer the device is being used in 3 NHS hospitals.

Because Cellvizio is used as an adjunct to EUS-FNA there would be no need to change the way current services are delivered if the system were adopted. Training is needed to operate the system. No other additional facilities or technologies are needed alongside the technology.

No published evidence on the resource consequences of adopting Cellvizio for the relevant indication was identified in the systematic review of evidence.

### *Strengths and limitations of the evidence*

In general, the studies considered in this briefing are small feasibility or pilot studies to establish technical feasibility, safety, diagnostic criteria, and diagnostic accuracy. All the studies included prospectively selected cohorts including 1 retrospective analysis of a prospectively selected cohort. No randomised controlled trials were identified.

Most sample sizes were relatively small, ranging from 18 (Konda et al. 2011) to 57 (Konda et al. 2013). The studies included 138 patients in total. No studies reported the use of a sample size calculation. Smaller sample sizes can lower the power and generalisability of a study.

Two studies were based in the USA (Konda et al. 2011; Nakai et al. 2015), 1 was a multinational study based in the US and France (Konda et al. 2013), and 2 studies were based in France (Napoleon et al. 2015a; Napoleon et al. 2015b). No published results of UK-based studies were found. The reported studies may not be generalisable to the NHS. A UK-based multicentre clinical trial is currently ongoing with an expected completion date of July 2017.

All 3 studies assessing diagnostic accuracy (Konda et al. 2013; Napoleon et al. 2015a; Nakai et al. 2015) used blinded-consensus review to compare Cellvizio with the reference standard. In Nakai et al. (2015), the investigator assessing image quality was not blinded to other clinical information. In Konda et al. (2013) and Napoleon et al. (2015a) investigators carrying out consensus review of images to obtain diagnostic criteria for pancreatic cysts were not blinded. Blinding minimises observer bias.



None of the studies carried out direct parallel comparisons of Cellvizio with EUS-FNA. All studies assessed Cellvizio during an EUS-FNA procedure. Only Nakai et al. (2015) provided an in-study comparison, but each patient had EUS with cystoscopy (SpyGlass), followed by nCLE (Cellvizio), and then FNA sequentially within the same procedure. Tissue trauma caused by invasive imaging procedures may have affected the results of any subsequent tests.

Pancreatic cysts have heterogeneous pathology and this contributes to challenges in diagnosis. The reference standard used to produce a final diagnosis varied between the studies. In all 3 studies assessing diagnostic accuracy, the final diagnosis was based on either a stringent gold standard (histopathology or positive cytology) or a committee consensus based on all available information including clinical presentation, combined with image findings from EUS, CT, and MRI, as well as fluid analysis and cytology from EUS-FNA. Study cohorts varied in the proportion of patients with a true criterion standard diagnosis by surgical histology compared with consensus review of non-surgical information. For example, in Nakai et al. (2015) only 2 of 30 patients had surgery and in Napoleon et al. (2015b) 20 of 33 patients had had surgery. This may produce challenges for direct comparison of the results because confidence levels, in particular for the less stringent methods, can vary.

The type of pancreatic cyst varies by gender. Serous cystadenomas and mucinous cystic neoplasms are predominantly found in women and intraductal papillary mucinous neoplasms and pseudocysts have similar prevalence in men and women. Nakai et al. (2015) and Napoleon et al. (2015a and 2015b) had more than twice the number of women than men in their sample, whereas in Konda et al. (2011 and 2013) the number of men and women included was about equal. In all studies, patients were recruited prospectively, but small sample sizes may result in cohorts being less representative of the wider population.

Cellvizio is designed to be used as an adjunct to standard EUS-FNA, so adverse events with Cellvizio may be expected to be similar to EUS-FNA. A prospective safety and feasibility study involving 128 people having EUS-FNA reported an overall complication rate of 2.4%, which included pancreatitis (de Jong et al. 2011). But, Konda et al. (2011 and 2013), Nakai et al. (2015) and Napoleon et al. (2015a) showed complication rates of between 3.2% and 11%. The smaller sample sizes may have amplified the results. In addition, Nakai et al. (2015) carried out 3 sequential procedures in their study. It is unclear which procedure (if any) caused the complications. A review by Krishna et al. (2016) found that combining data from the clinical trials described in Konda et al. (2011 and 2013), and Napoleon et al. (2015a) resulted in an overall rate of pancreatitis after the procedure of 4.3%, which is higher than in the de Jong et al. (2011) study. If there is prolonged contact of the needle probe with pancreatic tissue during Cellvizio imaging compared with

EUS-FNA alone, this may be related to an increased risk of pancreatitis. The comparative safety of Cellvizio with EUS-FNA needs further investigation.

The studies by Konda et al. (2011 and 2013) and Napoleon et al. (2015a and 2015b) were sponsored by the manufacturer. This introduces potential bias in the reporting of outcomes.

## Relevance to NICE guidance programmes

The use of the Cellvizio system is not currently planned into any NICE guidance programme.

NICE has issued the following guidance which is relevant to this briefing:

### Published guidance

[Suspected cancer: recognition and referral \(2015\) NICE guideline NG12](#)

### NICE advice

[The SpyGlass direct visualisation system for diagnostic and therapeutic procedures during endoscopy of the biliary system \(2015\) NICE medtech innovation briefing 21](#)

### NICE pathways

[Suspected cancer recognition and referral \(2015\) NICE pathway](#)

### Under development

[Pancreatic cancer, NICE guideline. Publication expected January 2018](#)

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## Appendix

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#### Table 1 Overview of the Konda et al. (2011) study

Study component	Description
Objectives/hypotheses	To evaluate the feasibility of nCLE during EUS-FNA of pancreatic lesions.
Study design	Single-centre, prospective, single-arm feasibility and safety study.
Setting	One tertiary care centre in the US. Dates of data collection not given. No follow-up period was specified.

Inclusion/exclusion criteria	<p>Inclusion:</p> <ul style="list-style-type: none"> <li>• people having EUS-FNA of pancreatic lesions.</li> </ul> <p>Exclusion:</p> <ul style="list-style-type: none"> <li>• people with a previous allergic reaction to fluorescein</li> <li>• people with renal insufficiency</li> <li>• women who were pregnant or breastfeeding.</li> </ul>
Primary outcomes	Feasibility and safety.
Statistical methods	Descriptive statistics were used to describe technical feasibility and safety. A 5-point Likert scale was used to evaluate image quality.
Patients included	n=18 (7 men, 11 women; mean age 57.9 years).
Results	<p>Images were obtained in 17 of 18 people. There were no device malfunctions. Technical challenges were encountered when imaging 6 of the 18 patients. Image quality was rated as good to very good in 10 of the 17 patients. Images from 5 patients were rated as moderate quality. Images were rated as low or poor quality for 2 patients.</p> <p>Sixteen of 18 patients had pancreatic cysts.</p> <p>Two serious adverse events occurred; both were pancreatitis needing hospitalisation.</p>
Conclusions	nCLE of the pancreas is technically feasible via a 19-gauge needle under endosonographic guidance.
Abbreviations: nCLE, needle-based confocal laser endomicroscopy; EUS-FNA, endoscopic ultrasound-guided fine needle aspiration.	

Table 2 Overview of the Konda et al. (2013) study

Study component	Description
Objectives/hypotheses	To assess both the diagnostic potential of nCLE in differentiating types of pancreatic cysts and the safety of the technique.

Study design	Single-arm, prospective, multicentre pilot study.
Setting	Patients were enrolled from 8 referral centres (6 in the US and 2 in Europe), between July 2010 and September 2011. No follow-up period was specified.
Inclusion/exclusion criteria	<p>Inclusion:</p> <ul style="list-style-type: none"> <li>• people having EUS-FNA for a pancreatic cyst and who were being considered for surgery.</li> </ul> <p>Exclusion:</p> <ul style="list-style-type: none"> <li>• people with renal insufficiency</li> <li>• people with an allergy to fluorescein.</li> </ul>
Primary outcomes	Diagnostic accuracy, sensitivity, specificity, PPV, NPV. Safety. Clinical diagnosis was made by clinical consensus (n=43) or histopathology (n=14).
Statistical methods	<p>Fisher's exact test was used to examine the association between pancreatic cysts diagnosed by surgical and non-surgical methods and features found by nCLE.</p> <p>Exact 95% CIs were constructed based on the binomial distribution.</p> <p>Descriptive statistics were carried out on safety data.</p>
Patients included	n=57 (32 men, 25 women; mean age 63.1 years).
Results	<p>Results from imaging in 26 patients were used to develop diagnostic terms for structures identified on nCLE.</p> <p>In 31 remaining patients, the presence of epithelial villous structures seen using nCLE was associated with potentially malignant cysts (<math>p=0.004</math>) and provided a diagnostic accuracy of 71% (95% CI 52 to 86), with a sensitivity of 59% (95% CI 36 to 79), specificity of 100% (95% CI 66 to 100), PPV of 100% (95% CI 75 to 100) and NPV of 50% (95% CI 26 to 74). No other features were significantly associated with potentially malignant cysts.</p> <p>The overall complication rate was 9% and included pancreatitis (n=1 mild, n=1 moderate), transient abdominal pain (n=1), and intracystic bleeding not requiring any further measures (n=3).</p>

Conclusions	The authors concluded that the preliminary data suggest that nCLE has a high specificity in the detection of potentially malignant cysts, but may be limited by low sensitivity.
Abbreviations: CI, confidence interval; EUS-FNA, endoscopic ultrasound-guided fine needle aspiration; nCLE, needle-based confocal laser endomicroscopy; NPV, negative predictive value; PPV, positive predictive value.	

Table 3 Overview of the Nakai et al. (2015) study

Study component	Description
Objectives/ hypotheses	To assess the feasibility, safety and diagnostic accuracy of combined nCLE and cystoscopy in the clinical diagnosis of potentially malignant cysts.
Study design	A single-centre, prospective, single-arm feasibility study.
Setting	An academic tertiary referral centre in the US. Dates of data collection not given. There was a follow-up period of 6 months to 2 years.
Inclusion/ exclusion criteria	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> <li>• people over 18 years with a pancreatic cyst.</li> </ul> <p>Exclusion criteria:</p> <ul style="list-style-type: none"> <li>• people contraindicated for EUS-FNA such as patients who were medically unstable, severe coagulopathy or poor visualisation on EUS for various reasons</li> <li>• women who were pregnant or breast-feeding</li> <li>• allergy to fluorescein</li> <li>• people with renal insufficiency.</li> </ul>
Primary outcomes	Technical feasibility and safety. Associations of cystoscopy and nCLE findings with clinical diagnosis of potentially malignant cysts. Clinical diagnosis was made by clinical consensus (n=28) or histopathology (n=2).

Statistical methods	Fisher's exact test was used to assess the association between imaging findings and clinical diagnosis. Diagnostic accuracy, sensitivity, specificity, PPV and NPV with a 95% CI were calculated. A Bonferroni adjustment was performed for multiple testing for associations of imaging findings and clinical diagnosis.	
Patients included	n=30 (9 men, 21 women; mean age 72 years [range 37 to 86 years]).	
Results	<p>The procedure was technically successful with the exception of 1 probe exchange failure. Image acquisition was 100% successful, with 90% of images being of excellent quality for nCLE and 67% for cystoscopy.</p> <p>Pancreatitis developed in 2 patients (7%) after the procedure.</p> <p>Specific features associated with the clinical diagnosis of mucinous cysts were identified: mucin on cystoscopy and papillary projections and dark rings on nCLE.</p>	
Accuracy: All patients		
	nCLE (%)	Cystoscopy (%)
Diagnostic accuracy	87 (range 72 to 87)	83 (range 69 to 83)
Sensitivity	77 (range 64 to 77)	71 (range 58 to 71)
Specificity	100 (83 to 100)	100 (83 to 100)
PPV	100 (83 to 100)	100 (82 to 100)
NPV	77 (64 to 77)	72 (60 to 72)
Accuracy: Subgroup of high certainty patients for mucinous cysts (n=18)		
	nCLE (%)	Cystoscopy (%)
Diagnostic accuracy	89 (range 68 to 89)	94 (range 75 to 94)
Sensitivity	80 (range 62 to 80)	90 (range 72 to 90)
Specificity	100 (77 to 100)	100 (78 to 100)
PPV	100 (77 to 100)	100 (80 to 100)
NPV	80 (62 to 80)	89 (69 to 89)

Conclusions	The imaging of pancreatic cysts by nCLE is useful in the clinical diagnosis of potentially malignant cysts.
Abbreviations: CI, confidence interval; EUS-FNA, endoscopic ultrasound-guided fine needle aspiration; nCLE, needle-based confocal laser endomicroscopy; NPV, negative predictive value; PPV, positive predictive value.	

Table 4 Overview of the Napoleon et al. (2015a) study

Study component	Description
Objectives/hypotheses	To identify and validate new diagnostic criteria for nCLE of pancreatic cysts and assess the diagnostic accuracy of nCLE to detect benign cysts (SCA).
Study design	Prospective, 3-centre, single-arm pilot study.
Setting	Three hospitals in France. Screening was carried out between June 2012 and March 2013. There was a follow-up period of 1 year.
Inclusion/exclusion criteria	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> <li>• a single cyst with diameter &gt;20 mm and with at least 1 cavity <math>\geq</math>13 mm in size.</li> </ul> <p>Exclusion criteria:</p> <ul style="list-style-type: none"> <li>• adults over 18 years</li> <li>• people with a known allergy to fluorescein</li> <li>• pregnancy</li> <li>• people having an EUS-FNA procedure within the past 3 months</li> <li>• people with chronic calcifying pancreatitis</li> <li>• people presenting with criteria for malignancy (tissue mass, metastases, ascites, vascular infiltration).</li> </ul>
Primary outcomes	Descriptive criteria for pancreatic cysts; diagnostic accuracy of nCLE for benign cysts (SCA). Clinical diagnosis was made by clinical consensus (n=13), positive FNA (n=11) or histopathology (n=7).

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Statistical methods	Diagnostic accuracy, sensitivity, specificity, PPV and NPV with a 95% CI were calculated. The interobserver variability was calculated using Fleiss' kappa statistics.
Patients included	n=31 (6 men and 25 women; mean age 54 years [range 24 to 76 years]).



Results	<p>A 'superficial vascular network' was identified as an nCLE criterion associated with benign cysts.</p> <p>Overall diagnostic accuracy (%; n=31):</p> <ul style="list-style-type: none"> <li>• diagnostic accuracy 87 (range 69 to 100)</li> <li>• sensitivity 69 (range 44 to 92)</li> <li>• specificity 100 (range 100 to 100)</li> <li>• PPV 100 (range 100 to 100)</li> <li>• NPV 82 (range 66 to 98).</li> </ul> <p>Subgroup analysis of patients with high certainty final diagnosis (%; n=18)<sup>a</sup>:</p> <ul style="list-style-type: none"> <li>• diagnostic accuracy 94</li> <li>• sensitivity 86</li> <li>• specificity 100</li> <li>• PPV 100</li> <li>• NPV 92.</li> </ul> <p>Subgroup analysis for patients with lower certainty final diagnosis (%; n=13)<sup>a</sup>:</p> <ul style="list-style-type: none"> <li>• diagnostic accuracy 77</li> <li>• sensitivity 50</li> <li>• specificity 100</li> <li>• PPV 100</li> <li>• NPV 70.</li> </ul> <p>Images were successfully acquired in all 31 people, with no technical failures reported. Mild acute pancreatitis was reported in 1 person.</p> <p>The interobserver agreement was substantial, kappa=0.77.</p>
Conclusions	<p>The authors conclude that the new nCLE criterion appears highly specific for the diagnosis of benign pancreatic cysts.</p>

Abbreviations: CI, confidence interval; FNA, fine needle aspiration; nCLE, needle-based confocal laser endomicroscopy; NPV, negative predictive value; PPV, positive predictive value; SCA, serous cystadenoma.

<sup>a</sup>Ranges not given.

**Table 5 Overview of the Napoleon et al. (2015b) study**

Study component	Description
Objectives/hypotheses	To determine new nCLE criteria for the diagnosis of pancreatic cysts, to propose a comprehensive nCLE classification for their characterisation, and to validate the performance of these criteria.
Study design	Retrospective analysis of single-arm prospective pilot study.
Setting	Three hospitals in France. Screening was carried out between June 2012 and March 2013. There was a follow-up period of 1 year.
Inclusion/exclusion criteria	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> <li>• a single cyst with diameter &gt;20 mm and with at least 1 cavity <math>\geq</math>13 mm in size.</li> </ul> <p>Exclusion criteria:</p> <ul style="list-style-type: none"> <li>• adults over 18 years</li> <li>• people with a known allergy to fluorescein</li> <li>• pregnancy</li> <li>• people having an EUS-FNA procedure within the past 3 months</li> <li>• people with chronic calcifying pancreatitis</li> <li>• people presenting with criteria for malignancy (tissue mass, metastases, ascites, vascular infiltration).</li> </ul>
Primary outcomes	Diagnostic yield and interobserver agreement. Clinical diagnosis was made by clinical consensus (n=13) or histopathology (n=20).

Statistical methods	Diagnostic accuracy, sensitivity, specificity, PPV and NPV with a 95% CI were calculated.  The interobserver variability was calculated using Fleiss' kappa statistics.
Patients included	n=33. Thirty-one of these people were also included in the Napoleon et al. (2015a) study, see <a href="#">table 4</a> . No further demographic information was provided for the additional 2 patients.
Results	New nCLE criteria were identified for MCN, PC and cystic NEN.  nCLE allowed a conclusive result to be drawn in 74% of patients. Of these, 87% were correct and 13% were incorrect when compared with the final diagnosis.  Interobserver agreement for cyst types was (kappa): <ul style="list-style-type: none"> <li>• MCN: 0.35</li> <li>• IPMN: 0.56</li> <li>• PC: 1.00</li> <li>• SCA: 0.88</li> <li>• all cysts: 0.72.</li> </ul>
Conclusions	The authors concluded that the new interpretation criteria with nCLE could facilitate the diagnosis of pancreatic cyst types.
Abbreviations: CI, confidence interval; NEN, neuroendocrine neoplasm; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; nCLE, needle-based confocal laser endomicroscopy; PC, pseudocyst; SCA, serous cystadenoma.	

## Search strategy and evidence selection

### Search strategy

#### For the clinical evidence

Pubmed (Ovid MEDLINE(R) 1946 to January Week 4 2016, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations February 05, 2016)

#### 1. Cellvizio.mp.

2. Microscopy, Confocal/ or Confocal laser endomicroscopy.mp.

3. Confocal laser microscopic imaging.mp.

4. Pancreatic Cyst/

5. Pancreatic Neoplasms/ or pancreatic cancer.mp.

6. 2 or 3

7. 4 or 5

8. 6 and 7

9. 1 or 8

10. remove duplicates from 9

11. limit 10 to (english language and humans and yr="2006 -Current")

Embase (Embase 1974 to 2016 February 05)

1. Cellvizio.mp.

2. Confocal laser endomicroscopy.mp. or confocal laser microscopy/

3. Confocal laser microscopic imaging.mp.

4. pancreas cyst/

5. pancreas cancer/

6. 2 or 3

7. 5 or 6

8. 6 and 7

9. 1 or 8

10. limit 9 to (human and english language and yr="2006 -Current")

#### For the economic evidence

Embase 1974 to 2016 March 02, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present; Searched on March 02, 2016

1. Cellvizio.mp.

2. confocal laser microscopy.mp.

3. Confocal laser endomicroscopy.mp.

4. 2 or 3

5. Confocal laser microscopic imaging.mp.

6. Pancreatic Cyst.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]

7. Pancreatic Neoplasms/ or pancreatic cancer.mp.

8. 4 or 5

9. 6 or 7

10. 8 and 9

11. 1 or 10

12. limit 11 to english language

13. limit 12 to human

14. limit 13 to yr="2006 -Current"

15. (cost\* or economic\*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]

16. 14 and 15

17. remove duplicates from 16

Cochrane Database of Systematic Reviews: Issue 3 of 12, March 2016

Database of Abstracts of Reviews of Effect: Issue 2 of 4, April 2015

Cochrane Central Register of Controlled Trials: Issue 2 of 12, February 2016

Health Technology Assessment Database: Issue 1 of 4, January 2016

NHS Economic Evaluation Database: Issue 2 of 4, April 2015

## *Evidence selection*

### **For the clinical evidence**

- Total number of publications reviewed: 64
- Total number of publications considered relevant: 27
- Total number of publications selected for inclusion in this briefing: 5

### **For the economic evidence**

- Total abstracts: 9
- Duplicates: 0
- Abstracts reviewed: 9
- Full papers reviewed: 2

Exclusion criteria: case studies, editorials, letters, reviews, conference proceedings/abstracts, animal studies, non-English language studies, studies not using Cellvizio

Studies for review: 0

## About this briefing

Medtech innovation briefings summarise the published evidence and information available for individual medical technologies. The briefings provide information to aid local decision-making by clinicians, managers and procurement professionals.

Medtech innovation briefings aim to present information and critically review the strengths and weaknesses of the relevant evidence, but contain no recommendations and are **not formal NICE guidance**.

## *Development of this briefing*

This briefing was developed for NICE by King's Technology Evaluation Centre. The [interim process and methods statement](#) sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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## Declarations of interest

No relevant interests declared.

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