Review of application of PillCam® capsule endoscopy (formerly known as M2A®) for the surveillance of Peutz-Jeghers syndrome

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Assessed by IMS Health, Sydney

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Summary

This assessment provided an evaluation of the limited evidence available for the use of capsule endoscopy in the surveillance of Peutz-Jeghers syndrome.

Safety

The studies included in this assessment concur that capsule endoscopy is a safe, well-tolerated procedure. Only very minor adverse events were reported, such as mild pain or discomfort, by one patient in a group of 19 (Brown et al 2005); one patient from a cohort of 11 required endoscopic removal of the capsule which was blocked due to a bowel obstruction (Schulmann et al 2005); and one patient reported by Thompson and colleagues (2006) was unable to swallow the capsule. (The capsule was subsequently placed in the stomach endoscopically).

Positive patient response when undergoing capsule endoscopy is potentially another indication of the tolerability of capsule endoscopy. Surveys conducted by Brown et al (2005) demonstrate a low complication rate and favourable patient reaction.

Exposure and accumulation of ionising radiation is eliminated by the use of capsule endoscopy as a substitute to small bowel radiography (Schulmann et al 2004) although no data to confirm this assertion was presented in this study.

Overall, the literature indicates that capsule endoscopy is a safe method for use in the monitoring and management of PJS (Soares et al 2004; Brown et al 2005; Thomson et al 2006).

Effectiveness

The small body of literature published on the effectiveness of capsule endoscopy in PJS surveillance limits the scope of analysis that can be performed to assess this technology's clinical effectiveness. Investigation of comparative effectiveness of capsule endoscopy is limited because there is no agreed reference standard. Among identified studies that considered the use of capsule endoscopy for PJS, five

mentioned some form of comparable technology. The most commonly studied comparator was small intestine x-ray, specifically, barium follow-through.

Capsule endoscopy is generally considered to be less invasive than comparative methods such as colonoscopy and enteroscopy, and most patients have expressed preference for capsule endoscopy over barium follow-through (Brown et al 2006; Soares et al 2005).

In five comparative studies, capsule endoscopy detected a greater number of gastrointestinal polyps than the comparative technique. Capsule endoscopy detected a median of four significant polyps in comparison with small bowel radiography, which detected only one (Brown et al 2005). Capsule endoscopy also detected more polyps than magnetic resonant imaging (MRI): 448 polyps were identified using capsule endoscopy, compared with 24 identified by MRI (Caspari et al 2004).

Capsule endoscopy accuracy issues were reported in one study as location and determination of size of polyps was less accurate using capsule endoscopy than with MRI (Caspari et al 2004).

Management

Investigations with capsule endoscopy have resulted in changes to patient management. Previous negative radiographic examinations have been proven to be false negatives by capsule endoscopy. Endoscopic and surgical resection of all visualised small bowel polyps was then necessary in these patients, altering their management (Burke et al 2005).

Furthermore, in a study by Schulmann et al (2005) all symptomatic patients with Peutz-Jeghers syndrome were referred for surgery after investigation with capsule endoscopy.

Recommendation

MSAC recommends that public funding be supported for performing capsule endoscopy, no more than once in any two year period, for small bowel surveillance in patients diagnosed with Peutz-Jeghers syndrome.
-The Minister for Health and Ageing accepted this recommendation 20 May 2008.-

Introduction

This review of the application for capsule endoscopy for application in monitoring Peutz-Jeghers syndrome (PJS) was performed to address the following objectives:

1. to confirm the evidence presented in the capsule endoscopy application
2. to provide a comprehensive summary based on a review of the literature of other evidence related to PJS
3. to provide an estimate of the number of people likely to be eligible for treatment.

Peutz-Jeghers syndrome

Peutz-Jeghers syndrome (PJS) is a rare genetic disorder that is characterised by hamartomatous polyps of the gastrointestinal tract and mucocutaneous melanin deposition. PJS is thought to be caused by nucleotide substations which result in splice site mutations and mRNA variants in the gene *STK11* (also known as *PJS* and *LKB1*) on chromosome 19. However, the disease is also known to occur spontaneously (Parsi et al 2004).

PJS symptoms include pain, bleeding, anaemia, intussusception and intestinal obstruction. Patients are usually diagnosed during childhood when they present with symptoms such as blue pigmentation and abdominal pain. People with PJS are known to have a higher incidence of cancer. Cancers can be intestinal—gastrointestinal polyps are prone to malignant conversion—and extra-intestinal (Parsi et al 2004).

People with PJS are therefore recommended to follow a monitoring protocol for the course of their lifetimes at two to three year intervals. Small bowel radiography (gastroscopy, colonoscopy and barium follow-through) are the current suggested monitoring techniques for people living with PJS (McGarrity 2000; Tomlinson 1997). Sensitivity of barium follow-through is relatively poor, and there are clinical concerns about radiation accumulation over a lifetime of surveillance using small bowel radiography methods. These concerns may contribute to less assiduous

adherence to monitoring protocols involving barium follow-through in practice (Schulmann et al 2004).

Patient management

Diagnosis of Peutz-Jeghers syndrome (PJS) is usually established after the patient presents with symptoms such as pain, bleeding, anaemia, intussusception or intestinal obstruction. Most diagnoses are made during childhood, although some patients do not present until they reach their 20s or 30s.

Following confirmation of PJS diagnosis, multidisciplinary patient management provides effective education, counselling and monitoring. Genetic counselling and genetic testing is often offered to PJS patients as a component of multidisciplinary management, and can provide advice and information to patients and their families on symptoms, cancer risks, treatments and surveillance options.

The management of PJS should include surveillance of gastrointestinal polyps and skin lesions or pigmentations. Surveillance aims to minimise the risk of developing intestinal cancers, obstructions or bleeding (Melmed et al 2005; Parsi et al 2004). Current recommendations for surveillance include:

- upper gastrointestinal endoscopy (approximately biennially) and removal of polyps (hamaratomas)
- colonoscopy (approximately triennially)
- small bowel radiography particularly barium follow-through (approximately biennially)
- elective polypectomy
- annual mammography; scrotal ultrasound; cervical smear
- regular breast self examination; testicular self examination.

(McGarrity et al 2000; Tomlinson and Houlston 1997).

Capsule endoscopy

The PillCam® capsule endoscope is roughly the size of a vitamin pill (11 x 26 mm). It is administered after a period of 10–12 hours fasting and moves through the digestive system over approximately eight hours, capturing two images every second.

About 50,000 images are taken during the eight hours the camera takes to pass through the small bowel by peristalsis. Images are transmitted to and recorded by a unit worn at the waist (DataRecorder™) from eight sensors placed on the patient's abdomen. Images are downloaded from the DataRecorder™ to a computer and analysed by clinicians. After 24–72 hours the capsule endoscope is passed from the body during a bowel movement and is entirely disposable.

Eligible population

Incidence of Peutz-Jeghers syndrome

Peutz-Jeghers syndrome is classified as a rare genetic disease. Global estimates of the affected population vary, but according to Parsi and colleagues (2004) 1 in 120,000 live births are affected by PJS. Other estimates indicate a wider range of incidence—1 in 50,000 to 1 in 200,000 as reported by Terauchi et al (2006). According to data published by the Cancer Institute NSW (www.cancerinstitute.org.au/cancer_inst/programs/pjs.html) the incidence of Peutz-Jegher syndrome is between 1 in 160,000 and 1 in 280,000.

Uncertainties about incidence mean that it is difficult to accurately estimate the eligible population. There are no Australian-specific prevalence data. If the full range of incidence is considered, the number of people affected by PJS in Australia could be from 71 (1 in 280,000) to 400 (1 in 50,000) making this a rare condition in the population.

Surveillance of small bowel polyps is currently recommended to be carried out every two years (McGarrity et al 2000; Tomlinson and Houlston 1997). Therefore the number of procedures performed per year potentially range from 36 to 200. Capsule endoscopy for the management of PJS would be required infrequently because of the small number of people affected.

Approach to assessment

A literature search strategy was devised (Appendix A) to identify all relevant published articles relating to the capsule endoscopy and Peutz-Jeghers syndrome.

The EMBASE and Medline databases were searched (9 October 2007, via the EMBASE.com interface) using key terms including:

- capsule endoscopy; capsule endoscopes; endoscopes, gastro-intestinal
- video recording; image enhancement; digestive system; wireless imaging
- M2A; pillcam or pill cam; given imaging
- hamartomatous intestinal polyps; pigmented spot polyposis; peutz-jeghers syndrome; intestinal polyposis.

The literature search identified 55 references overall. Titles and abstracts for the articles identified by this systematic literature search were reviewed and exclusions made as required. Full text articles were retrieved for all other references.
All articles were reviewed and some were excluded due to further criteria:

Table 1 Exclusion and inclusion criteria

Reviewed	Exclusion criteria
Title and abstract	Exclude: Single patient (case) study Exclude: Report on the wrong technology Exclude: Report on the wrong patient group Exclude: Editorials, opinions or letters
Full text	Exclude: Foreign language Exclude: Review or letter Exclude: Inadequate data Exclude: Report on the wrong technology
Reviewed	**Inclusion criteria**
Full text	Comparative study Relevant patient group and correct technology Relevant review of Peutz-Jeghers *and* Relevant review of capsule endoscopy

Included articles are summarised in Table 4.

Further to the systematic review of the literature, the application made on behalf of Given Imaging was studied and comparisons were made between the evidence in

the original application and the literature search described above. Any additional, relevant articles mentioned in the application were retrieved and appraised. The appraisal and exclusion criteria for these additional citations are recorded in Table 4.

Study appraisal

The ideal design for a study of the comparative accuracy of diagnostic tests is one in which each test is performed in a population with a defined clinical presentation, in a consecutive series. The study should be an independent, blinded comparison with a valid reference standard (NHMRC 2005).

Assessment of eligible studies

Evidence retrieved from the literature searches were assessed according to the NHMRC levels of evidence dimensions of evidence (Table 2) where applicable.

Table 2 NHMRC levels of evidence

Level	Diagnosis[b]
I[a]	A systematic review of level II studies
II	A study of test accuracy with: an independent, blinded comparison with a valid reference standard[c] among consecutive patients with a defined clinical presentation[d]
III-1	A study of test accuracy with: an independent, blinded comparison with a valid reference standard[e] among non-consecutive patients with a defined clinical presentation[f]
III-2	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence
III-3	Diagnostic case-control study
IV	Study of diagnostic yield (no reference standard)

Source: NHMRC (2005)

[a] A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence

[b] The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes. See MSAC (2004) Guidelines for the assessment of diagnostic technologies. Available at: www.msac.gov.au

[c] The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study. See Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Medical Research Methodology* 2003, 3: 25

[d] Well-designed population based case-control studies (eg. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias because the spectrum of study participants will not be representative of patients seen in practice

[e] Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard

Results

There were 55 studies identified by the literature search; nine satisfied inclusion criteria described in *Approach to assessment*. The inclusion criteria stated that studies must be:

- comparative, or, due to the limitations of the literature available
- an investigation of the correct patient group and technology (ie Peutz-Jegher syndrome and capsule endoscopy).

A further three reviews were included in the assessment because they were considered to contain relevant information specifically about Peutz-Jeghers syndrome and the use of capsule endoscopy. Of the included studies, five were comparative. Four compared capsule endoscopy to barium follow-through (barium meal with small bowel radiography) and one compared capsule endoscopy with magnetic resonance imaging (MRI). The four remaining studies were non-comparative.

Table 3 Included studies

Author (year) Country Study design	Study characteristics	Test characteristics	Outcomes	Study quality[a]
Brown (2005) UK Prospective Unclear enrolment Unclear blinding	19 PJS patients Diagnosing the presence of polyps in patients known to have PJS (comparing two methods for the ability to detect of GI polyps > 1 cm)	Prior procedures: 10 patients reported to have prior barium follow-through Capsule endoscopy: Given Imaging PillCam Comparator: Barium follow-through (small bowel radiography)	Primary outcome was detection of significant polyps Greater number of >1 cm polyps captured by PillCam than radiography (range 0–18 compared with 0–4). Patient preference was for PillCam over barium, based on comfort and convenience. Estimation of polyp size was less accurate with PillCam	IV

Author (year) Country Study design	Study characteristics	Test characteristics	Outcomes	Study quality[a]
Burke (2005) USA Prospective Consecutive No blinding	4 PJS patients in a mixed population of 19 Patients included for the monitoring of PJS	Prior procedures: all PJS patients had previously undergone laparoscopy Capsule endoscopy: Given Imaging PillCam Non-comparative	75% PJS patients had polyps beyond the duodenum ranging from 0.2–30 mm. 2 patients had diffuse polyposis, 1 patient had polyposis in the ileum only. In 2 patients findings with capsule endoscopy led to further procedures eg surgery or intra-operative endoscopy In one patient the capsule endoscopy failed (did not reach colon)	IV
Caspari (2004) Germany Prospective Consecutive Blinded	4 PJS patients in a mixed population of 20 Test of effectiveness of capsule endoscopy compared to magnetic resonance imaging for the monitoring of hereditary polyposis syndromes	Prior procedures: not reported Capsule endoscopy: Given Imaging PillCam Comparator: magnetic resonance imaging	448 polyps (from all 4 patients) detected by capsule endoscopy ranging in size from 1 mm–30 mm. MRI detected 24 polyps (from the same 4 patients) none smaller than 5 mm Individual patient data not provided Capsule endoscopy is able to detect smaller polyps. MRI determines size and location more accurately	IV
Mata (2005) Spain Prospective Consecutive Blinded	4 PJS patients in a mixed population of 24 Diagnosing the presence of polyps in patients known to have PJS (comparing two methods for the ability to detect GI polyps)	Prior procedures: 1 PJS patient previously had segmentary small bowel resection Capsule endoscopy: Given Imaging PillCam Comparator: barium follow-through (small bowel radiography)	3 PJS patients had small bowel polyps discovered by both capsule endoscopy and barium follow-through Capsule endoscopy identified more polyps 14, 5 and 9 polyps were discovered in the 3 patients respectively in comparison to Barium follow through, which discovered 4, 3 and 5 polyps in the same three patients	IV
Mezoff (2006) USA Prospective Unclear enrolment Unclear blinding	1 PJS patient in a mixed population of 2 Patient included for the investigation of the cause of PJS symptoms	Prior procedures: PJS patient had previous surgery to remove a polyp Capsule endoscopy: Given Imaging PillCam Comparator: Small bowel radiography (used to diagnose unsuccessfully before capsule endoscopy)	Correct diagnosis of a large polyp in the small intestine (missed by small bowel series). Removal of this polyp relieved symptoms	IV

Author (year) Country Study design	Study characteristics	Test characteristics	Outcomes	Study quality[a]
Schulmann (2004) Germany Prospective Unclear enrolment Unclear blinding	10 patients (all PJS) Patients included for the monitoring of PJS	Prior procedures: Not reported Capsule endoscopy: Given Imaging PillCam Non-comparative	5 patients had multiple large polyps, all were admitted to surgery; of the other 5 patients, 1 had no polyps detected by capsule endoscopy and 4 had only a few polyps which were removed by polypectomy	IV
Schulmann (2005) Germany Prospective Consecutive Unclear blinding	11 PJS patients in a mixed population of 43 Patients were included in study for surveillance (n=32), genetic counselling (n=11) and surgery (n=1). All 43 patients offered capsule endoscopy	Prior procedures: 10/11 PJS patient previously had segmentary small bowel resection Capsule endoscopy: Given Imaging PillCam Non-comparative	1 x patient with no pathologic findings; 2 x patients with 1 polyp discovered; 1 patient with 2 polyps discovered; 1 patient with 3 polyps; 1 patient with 10 distal polyps; 1patient with 19 polyps; 1 patient with 23 polyps; 1 patient with >30 polyps; and 2 with > than 100 polyps	IV
Soares (2005) Portugal Prospective Non-consecutive No blinding	14 patients with GI polyposis (probable PJS) in a mixed population of 20 Patients included for the diagnosis and monitoring of PJS	Prior procedures: not reported Capsule endoscopy: Given Imaging PillCam Non-comparative	7 patients out of the 14 with GI polyposis had at least one large polyp (>11 mm) discovered by capsule endoscopy. All 14 had multiple polyps	IV
Thomson (2005) UK Prospective Consecutive Blinded	3 PJS patients in a mixed population of 28 Patients included for the diagnosis and monitoring of PJS	Prior procedures: Upper GI endoscope and ileocolonoscopy Capsule endoscopy: Given Imaging PillCam Comparator: barium follow-through (small bowel radiography)	2 of the 3 patients with PJS had small bowel polyps detected that were not identified by radiography; both had polyps blocking the entire lumen that were not detected by radiography; both patients' continued management was altered based on capsule endoscopy findings 1 patient had difficulty swallowing the capsule and it was placed in the stomach endoscopically	IV

Abbreviations: PJS, Peutz-Jegher syndrome; GI, gastro-intestinal; MRI, magnetic resonance imaging

[a] According to NHMRC levels of evidence for diagnostic tests

The original application presented several studies as evidence. These studies were also identified in the literature review, retrieved and considered for inclusion using previously agreed criteria. These studies were excluded for the reasons described (Table 4):

Table 4 Studies presented in original application—reasons for exclusion

Author (year) Country	Title	Reason for exclusion
De Palma (2004) Italy	Small bowel polyps in Peutz-Jegher's syndrome: Diagnosis by wireless capsule endoscopy	Excluded: inadequate data
De Palma (2004) Italy	Minimally invasive diagnosis of Peutz-Jegher's syndrome	Excluded: inadequate data
Heine (2006) USA	Milestone in gastrointestinal endoscopy: Double-balloon enteroscopy of the small bowel	Excluded: wrong technology
Lopes (2005) Portugal	Peutz-Jegher's syndrome: variability of gastro-intestinal expression at pediatric age	Excluded: foreign language
Maluenda (2006) Spain	Capsule endoscopy in a 15-year-old boy with Peutz-Jegher's syndrome	Excluded: case study
Pennazio (2004) Italy	Small bowel endoscopy	Excluded: review or letter
Pennazio (2005) Italy	Small-intestinal pathology on capsule endoscopy: tumors	Excluded: single patient (case) study
Pennazio (2006) Italy	Capsule endoscopy: Where are we after 6 years of clinical use?	Excluded: review or letter
Perez-Cuadrado (2006) Spain	Double balloon enteroscopy: a descriptive study of 50 explorations	Excluded: wrong technology
Terauchi (2006) USA	Double balloon endoscopy and Peutz-Jegher's syndrome: a new look at an old disease	Excluded: wrong technology

Due to the limitations of the literature available, no systematic reviews on the use of capsule endoscopy for the surveillance of Peutz-Jeghers syndrome were available. However, the reviews listed in Table 5 are considered here as supportive information as the correct technology and relevant condition were described.

Table 5 Included non-systematic reviews

Author (year) Country	Title
Melmed (2005) USA	Capsule endoscopy: practical applications
Parsi (2004) USA	Utility of capsule endoscopy in Peutz-Jegher's syndrome
Lynch (2006) USA	Video capsule endoscopy: What is the role in surveillance of hereditary colon cancer syndromes

Safety

Safety data were reported in five studies: three were comparative studies and two were non-comparative. Brown et al (2005) reported that all 19 patients in the study swallowed, tolerated and passed the capsule endoscope without any adverse effects or complications. There was one patient in this study who reported mild discomfort after capsule endoscopy.

Schulmann et al (2004) reported the safety of capsule endoscopy in comparison to radiography. These investigators suggested that capsule endoscopy is a safer procedure for monitoring PJS patients as it avoids the accumulation of radiation caused by regular barium follow-through (Schulmann et al 2004). No data were reported to support this claim.

Schulmann and colleagues (2004) also reported a low complication rate, with only one patient out of the total study population (n=11) requiring endoscopic removal of the capsule due to an obstruction in the bowel which blocked its passage (Schulmann et al 2005).

In the study by Thomson et al (2006), one of three PJS patients could not swallow the capsule and it was placed in the stomach endoscopically. No other complications were reported. Soares et al (2005) also reported no complications or adverse events with any of the patients in their investigation (n=14).

Effectiveness

Brown et al (2005) used a follow-up questionnaire after patients received both capsule endoscopy and barium follow-through. This questionnaire demonstrated that this cohort had a significant preference to be monitored by capsule endoscopy: Sixteen of 17 patients who took part in this questionnaire said they would prefer capsule endoscopy in the future. Capsule endoscopy scored higher than barium follow-through for both comfort and convenience (98 and 90, respectively, interquartile range [IQR]).

Evidence from the study by Soares et al (2005) confirms patient preference: it was reported that all patients in their investigation described the procedure as comfortable and were willing to have the procedure repeated.

All of the included studies found that capsule endoscopy was as effective and in most cases more effective in detecting small bowel polyps. Capsule endoscopy detected more polyps than the comparator in all comparative studies (Brown et al 2005; Caspari et al 2004; Mata et al 2005; Mezoff et al 2005; Thomson et al 2005).

The use of prior tests or procedures in some of these studies (Brown et al 2005; Caspari et al 2004; Mata et al 2005; Mezoff et al 2006; Soares et al 2005; Thomson et al 2005) suggests that the included PJS population may represent patients with a more severe form of the disease than a monitored incident population. Therefore, the results for PillCam® in these patients may be less applicable to those seen in clinical practice.

In the study by Caspari et al (2004), 448 polyps were detected in four patients (patient 1=187 polyps; patient 2=46 polyps; patient 3=126 polyps; patient 4=84 polyps). MRI found only 24 polyps in the same four patients (patient 1=8 polyps; patient 2=5 polyps; patient 3=6 polyps; patient 4=5 polyps).

Management

Investigations with capsule endoscopy resulted in changes to patient management, as reported in the non-comparative study by Burke et al (2005). Previous radiographic examination had been negative, but capsule endoscopy detected polyps that required patients (n=2) to undergo endoscopic and surgical resection of all visualised small bowel polyps.

Mata et al (2004) also claimed that correct identification of small bowel polyps led to changes in the management of patients in a mixed population. However, it was not possible to determine how management had changed for PJS patients due to inadequate data reporting.

In the study by Schulmann et al (2005), all symptomatic PJS patients were subsequently admitted for surgery after confirmation of polyps by capsule endoscopy which had been out of range of push enteroscopy (n=3) or because of the high polyp burden detected by capsule endoscopy (n=2).

Conclusions

The evidence is somewhat limited for the assessment of capsule endoscopy in the surveillance of Peutz-Jeghers syndrome, mainly because of the small patient population, due to the rarity of the condition, and because the technology is comparatively new (all included studies are from the 2004–2006 period).

The evidence presented in this assessment indicates that capsule endoscopy is a safe method for the surveillance and management of Peutz-Jeghers syndrome (Soares et al 2004; Brown et al 2005; Schulmann et al 2005; Thomson et al 2006). Schulmann et al (2004) proposed that exposure and accumulation of ionising radiation was eliminated by the use of capsule endoscopy as a substitute to small bowel radiography. (No supporting data were provided).

The comparative studies identified in this assessment indicate that capsule endoscopy is better at detecting the number of polyps and extent of polyposis. The technology is somewhat limited in terms of accurately locating and determining the size of polyps (Caspari et al 2004). Clinically significant polyps were considered to be greater than 15 mm diameter in this study (which MRI was able to detect as efficiently as capsule endoscopy).

Patient tolerance and preference is a favourable aspect of this technology over its comparators. The procedure is well tolerated by patients, and it has very few minor side effects. Most patients have expressed preference for capsule endoscopy over barium follow-through (Brown et al 2006; Soares et al 2005).

Due to low quality or inadequate data reporting, inclusion of data derived from professional opinion, and summaries or abstracts only from literature in the original application did not contribute usable evidence in support of capsule endoscopy (such as Macrae et al 2006). Unpublished data cited in the original application could not be considered because data accuracy could not be verified. However, the original application included all studies presented in Table 3 (apart from the study by Thomson et al 2006).

The application claimed that capsule endoscopy would be a suitable, safe and effective method for monitoring patients with Peutz-Jeghers syndrome. This opinion is generally supported by the limited evidence available in the literature.

Recommendation

MSAC has considered the safety of capsule endoscopy for the small bowel surveillance of Peutz-Jeghers syndrome (PJS) and has determined that it is a safe, well-tolerated procedure compared with small bowel surveillance by barium follow-through radiography.

The small body of literature published on the clinical effectiveness of capsule endoscopy in small bowel surveillance of PJS limits the scope of analysis that can be performed to assess this technology. However, MSAC finds that this procedure is changing patient management in situations where radiographic examinations have been demonstrated to produce false negative results. MSAC finds that capsule endoscopy for small bowel surveillance of PJS is likely to be as effective and as cost-effective as small intestine x-ray.

MSAC recommends that public funding be supported for performing capsule endoscopy, no more than once in any two year period, for small bowel surveillance in patients diagnosed with Peutz-Jeghers syndrome.

-The Minister for Health and Ageing accepted this recommendation 20 May 2008.-

Appendix A

Table 6 Excluded studies

Author (year)	Title	Exclusion criteria
Akman (2005)	A combination of small bowel imaging methods: Conventional enteroclysis with complementary magnetic resonance enteroclysis	Exclude: wrong technology
Classen (1973)	Present status of enteroscopy	Exclude: wrong technology
Davies (1995)	Diagnostic and therapeutic push type enteroscopy in clinical use	Exclude: wrong technology
Edwards (2003)	Long-term results of polyp clearance by intra-operative enteroscopy in the Peutz-Jegher's syndrome	Exclude: wrong technology
Heine (2006)	Milestone in gastrointestinal endoscopy: Double-balloon enteroscopy of the small bowel	Exclude: wrong technology
Honda (2006)	An increase in the serum amylase level in patients after per oral double-balloon enteroscopy: An association with the development of pancreatitis	Exclude: wrong technology
Lo (2006)	Therapeutic uses of double-balloon enteroscopy	Exclude: wrong technology
Perez-Cuadrado (2002)	Oral access to the small bowel	Exclude: wrong technology
Perez-Cuadrado (2007)	Training and new indications for double balloon endoscopy	Exclude: wrong technology
Barussaud (2006)	Clinical spectrum and surgical approach of adult intussusceptions: A multi-centric study	Exclude: wrong patient group
Farrell (2002)	Intraductal papillary mucinous tumour of the pancreas	Exclude: wrong patient group
O'Loughlin (2004)	Wireless capsule endoscopy	Exclude: wrong patient group
Schulmann (2003)	Diagnosing small bowel Crohn's disease with wireless capsule endoscopy (multiple letters)	Exclude: wrong patient group
Soares (2003)	Ascariasis observed by wireless-capsule endoscopy	Exclude: wrong patient group
Gay (2006)	What's new in video-capsule endoscopy	Exclude: foreign language
Holm (2004)	Capsule endoscopy—A new imaging method in gastroenterology	Exclude: foreign language
Plum (2007)	Polyps of the small bowel in patients with Peutz-Jegher's syndrome: Recommendations for diagnosis and treatment	Exclude: foreign language
Sass (1999)	Colon carcinoma: Early detection and aftercare	Exclude: foreign language
Caronna (2003)	Acute abdomen in a 15-year-old patient with Peutz-Jegher's syndrome: Surgical approach	Exclude: single patient (case) study
Kam (2006)	Peutz-Jjegher's syndrome diagnosed in a schizophrenic patient with a large deletion in the STK11 gene	Exclude: single patient (case) study
Lopes (2004)	A. Peutz-Jegher's syndrome: Variability of gastrointestinal expression at pediatric age	Exclude: single patient (case) study
Lorenzo-Zuniga (2006)	The utility of wireless capsule endoscopy, as compared with barium contrast study, in a case of Peutz-Jegher's syndrome	Exclude: single patient (case) study; Exclude: review (letter)
Maluenda (2007)	Capsule endoscopy in a 15-year-old boy with Peutz-Jegher's syndrome	Exclude: single patient (case) study

Author (year)	Title	Exclusion criteria
Mangili (2004)	An unusual admixture of neoplastic and metaplastic lesions of the female genital tract in the Peutz-Jegher's syndrome	Exclude: single patient (case) study
Schulmann (2007)	The patient with multiple intestinal polyps	Exclude: single patient (case) study
Enns (2006)	Who would I consider for capsule endoscopy?	Exclude: review (opinion)
Mihaly (2005)	Gastrointestinal manifestations of common variable immunodeficiency diagnosed by video- and capsule endoscopy	Exclude: review (letter)
Rey (2006)	European Society of Gastrointestinal Endoscopy (ESGE) video capsule endoscopy: Update to guidelines	Exclude: review (guidelines)
Seidman (2002)	Wireless capsule video-endoscopy: An odyssey beyond the end of the scope	Exclude: review or letter
Valette (2004)	Cross sectional imaging evaluation of the small bowel	Exclude: review
Von Allmen (2006)	Progress in understanding and treatment	Exclude: review
Wong (2007)	Response	Exclude: review, editorial, opinion piece
Makins (2006)	Guidelines for capsule endoscopy: Diagnoses will be missed	Exclude: inadequate data

Table 7 Literature search strategy used to search EMBASE.com for capsule endoscopy in the surveillance of Peutz-Jeghers syndrome

	Keywords
1	"capsule endoscopy"
2	"capsule endoscope"
3	"video capsule endoscopy"
4	"esophageal capsule endoscopy"
5	"string wireless capsule endoscopy"
6	"wireless capsule endoscopy"
7	endoscope
8	device
9	"drug capsule"
10	"medical instrumentation"
11	"diagnostic imaging"
12	videorecording
13	"imaging system"
14	#7 or #8 or #9 or #10 or #11 or #12 or #13
15	"gastrointestinal endoscopy"
16	endoscopy
17	enteroscopy
18	gastroscopy
19	#15 or #16 or #17 or #18
20	#13 and #19
21	"capsule endoscopy"
22	"capsule endoscope"
23	(capsule or wireless) and endoscop*
24	(capsule or wireless) and endoscop*
25	capsule and enteroscop*
26	capsule and enteroscop*
27	wireless and record*
28	wireless and record*
29	"disposable *3 imaging"
30	"ingestible *3 imaging"
31	"capsule *3 imaging"
32	m2a
33	pillcam or "pill cam"
34	"given *3 imaging"
35	"given *3 diagnostic" or "given *3 diagnostics"
36	#1 or #2 or #3 or #4 or #5 or #6 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35
37	"peutz jeghers syndrome"
38	"peutz *1 jeghers" or "peutz *1 jegher"
39	"intestinal polyposis 2" or "intestine polyposis 2"
40	"perioral lentiginosis" or "pigmented spot polyposis"
41	"hamartomatous intestinal polyposis"
42	"polyps *1 spots syndrome" or "mckusick 17520"
43	#37 or #38 ro #39 or #40 or #41 or #42
44	#36 and #43

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