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Australia and New Zealand Horizon Scanning Network

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TERRITORY GOVERNMENTS OF AUSTRALIA
AND THE GOVERNMENT OF NEW ZEALAND

Horizon Scanning Technology Prioritising Summary

Autofluorescence imaging for colonoscopic adenoma detection

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**Australian
Safety
and Efficacy
Register
of New
Interventional
Procedures -
Surgical**



**Royal Australasian
College of Surgeons**

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PRIORITISING SUMMARY

REGISTER ID

S000058

NAME OF TECHNOLOGY

**AUTOFLUORESCENCE IMAGING FOR
COLONOSCOPIC ADENOMA DETECTION**

PURPOSE AND TARGET GROUP

**INCREASE DETECTION/REMOVAL RATE OF
ADENOMA DURING COLONOSCOPIC SCREENING IN
PATIENTS AT RISK OF ADENOMA OR COLORECTAL
CANCER**

STAGE OF DEVELOPMENT (IN AUSTRALIA)

- | | | | |
|-------------------------------------|--------------------|--------------------------|------------------------------------------------------------------------|
| <input type="checkbox"/> | Yet to emerge | <input type="checkbox"/> | Established |
| <input type="checkbox"/> | Experimental | <input type="checkbox"/> | Established <i>but</i> changed indication or modification of technique |
| <input checked="" type="checkbox"/> | Investigational | <input type="checkbox"/> | Should be taken out of use |
| <input type="checkbox"/> | Nearly established | | |

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- | | | | |
|-------------------------------------|----------------|-------------|-----|
| <input type="checkbox"/> | Yes | ARTG number | N/A |
| <input checked="" type="checkbox"/> | No | | |
| <input type="checkbox"/> | Not applicable | | |

INTERNATIONAL UTILISATION

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
Canada	✓		
Germany	✓		
Japan			✓
Netherlands	✓		
Poland	✓		
United Kingdom	✓		
United States	✓		

IMPACT SUMMARY

Colonoscopy using autofluorescence imaging is an alternative to conventional white light colonoscopy for the detection of adenoma in patients at risk of developing colorectal cancer. The technology is currently in the investigational stage in Australia.

BACKGROUND

Colorectal cancer occurs when the growth of epithelial tissue in the inner lining of the colon (mucosa) accelerates, producing an abnormal growth or lesion known as a polyp. Polyps of glandular origin are called adenomas. Although polyps are benign tumours, they have the potential to become malignant. A malignant adenoma is called an adenocarcinoma. Since a pre-malignant lesion can quickly turn into a carcinoma, early detection of an adenoma is vital for preventing colorectal cancer in patients who are predisposed to the disease (Matyja et al. 2006). Both genetic and environmental factors can lead to the development of colorectal cancer (Mayinger et al. 2003). While some studies link the development of adenomas with inflammatory bowel disease, others consider that their formation has no particular trigger (Wang et al. 1999).

The standard method of detecting adenoma is optical colonoscopy (Uedo et al. 2007). This involves inserting a long, flexible endoscope (colonoscope) through the anus into the colon until it reaches the small intestine. As the endoscope is slowly withdrawn, the mucosal tissue is examined for adenomas, which are then biopsied. Traditionally, white light colonoscopy is used whereby the light source provides red, green and blue wavelength light sequentially by a rotation filter (Uedo et al. 2007). However, flat lesions are often difficult to identify with white light and diagnosis is usually dependent on random biopsies (Mayinger et al. 2003).

A novel technique, autofluorescence colonoscopy, has been developed to detect adenomas typically missed by white light colonoscopy. Autofluorescence colonoscopy works by exploiting the varying fluorescent characteristics of naturally occurring molecules found in tissues of the gastrointestinal tract (Haringsma et al. 2001). These molecules, known as fluorophores, include collagen, nicotinamide adenine dinucleotide, flavins and porphyrins (Haringsma et al. 2001). The concentration of endogenous fluorophores differs between tissues according to their thickness, micro-architecture, and haemoglobin concentration. Thus, the autofluorescence of normal mucosa is greater than that of diseased colonic tissue (Haringsma et al. 2001).

In fluorescent colonoscopy, two types of light are emitted through a rotation filter: excitation light (395 nm to 475 nm), which induces autofluorescence, and G'-light (550 nm) for taking reflection images (Uedo et al. 2007). The image processor depicts autofluorescence as green, and green reflects images to red and blue to produce composite images (Uedo et al. 2007). The net fluorescence intensity for normal mucosa is between 400 nm and 700 nm, which is approximately three times the intensity of diseased tissue. Thus, normal tissue is depicted as bright green, while potentially adenomatous tissue is displayed as magenta (the complement of green) (Wang et al. 1999). Haemoglobin is depicted as dark green (Uedo et al. 2007).

CLINICAL NEED AND BURDEN OF DISEASE

In 2003, cancer comprised 19% of Australia's total burden of disease (ABS 2006). Colorectal cancer is the second most common cancer among Australian men and women, with 12,844 new cases being reported in 2001 (AIHM 2006; Cancer Council of Australia 2007). Men and women have a one in 17 and a one in 26 chance of being diagnosed with colorectal cancer by the age of 74 (AIHW 2006). Age is an important contributing factor to the increasing risk, and 80% of diagnoses occur in patients with no genetic predisposition (AIHW 2006; Cancer Council of Australia 2007).

In 2001, 37% of all incidents of colorectal cancer resulted in death (AIHW 2006). The 5-year survival rate for patients with stage I colorectal cancer is 90%. This decreases to 87% in patients with stage II cancer and 57% in patients with stage III cancer (Cancer Council of Australia 2007).

DIFFUSION

A laser-induced autofluorescence endoscopic imaging system was developed for use in bronchoscopic procedures to detect early or pre-cancerous lesions within the lung. This system was approved by the US Food and Drug Administration (FDA) in September 1996 (FDA 2007). Since the principles of cancer detection using fluorescence in the lung and colon are essentially the same, another laser-induced autofluorescence endoscopic imaging system was developed for use in the gastrointestinal tract. However, this system is still undergoing trials and has not been approved by the FDA (Xillix ® 2007). Neither system is listed in the Australian Register of Therapeutic Goods. Autofluorescence colonoscopy is very popular in Japan, however has gained very little acceptance in Australia (personal communication 2008). Trials are currently being conducted in Canada, Japan, Europe, the United Kingdom, and the United States.

COMPARATORS

White light colonoscopy is the standard method for detecting adenoma in the colon to prevent colorectal cancer, and is the main comparator for autofluorescence colonoscopy.

There are several other colonoscopic techniques that exploit different types of light to detect adenoma in the colon, including the following.

- Narrow band imaging – an optical filter technique which improves the visualization of tissue structures by enhancing the absorbance and scattering of light. Blue (415 nm) and green (540 nm) light is used to display superficial capillary networks and subepithelial vessels, respectively (Olympus 2007).
- Drug-induced fluorescence imaging – in which fluorescence is caused by the selective uptake and retention of an exogenously administered fluorescent drug (e.g. hexaminolevulinate) by the diseased tissue (Haringsma et al. 2001).

SAFETY AND EFFECTIVENESS ISSUES

One randomised crossover trial (Uedo et al. 2007) and two non-randomised cross-sectional analytic studies (Brand et al. 1999; Matyja et al. 2006) comparing autofluorescence imaging with white light colonoscopy were identified by the literature searches.

In the randomised crossover study carried out by Uedo et al. (2007), patients underwent colonoscopic examination of the distal sigmoid colon and rectum for polyps (Uedo et al. 2007). A total of 64 patients were randomly assigned (method not specified) to either autofluorescence or white light imaging groups. A single colonoscopic imaging device that could be switched from the white light to autofluorescence mode was used. For the white light imaging group, patients underwent white light colonoscopy (findings recorded included size, type and location of abnormalities) first and then received autofluorescence colonoscopy, which was conducted by a different endoscopist who was unaware of the first screen's results. The order of imaging was reversed for patients in the autofluorescence group. The diagnostic ability of the techniques was verified by histological analysis of biopsy samples.

Brand et al. (1999) examined 12 men and 8 women (mean age: 60.5 years) who were due for screening. Twelve patients had colonic adenoma, six had inflammatory bowel disease, one had a history of colon cancer and one had a positive occult blood test. A single colonoscopic imaging device that could be switched from the white light to autofluorescence mode was used. White light colonoscopy was conducted first, then autofluorescence was used to assess areas of the colon determined to be "suspect for dysplasia" by white light examination. White light imaging classified tissue as either "suspect for dysplasia" or "not suspect for dysplasia"; autofluorescence then classified the same regions as either light-induced fluorescence endoscopy (LIFE) positive (diseased) or LIFE negative (normal). All suspect lesions were biopsied. The sensitivity and specificity of each method was calculated by correlating the results with histological findings (Brand et al. 1999).

Matyja et al. (2006) examined 51 patients with acromegaly for the presence of colonic polyps. Patients with acromegaly secrete excessive amounts of growth hormone and have an increased risk of colorectal adenoma. The group comprised 21 men and 30 women, none of whom had a personal or familial history of adenoma or colorectal cancer. The study design was divided into two phases where the colon was examined from the rectum to the caecum. Two colonoscopic devices, one for white light and one for autofluorescence, were used for each experimental group. In the first phase, the colon was examined under white light, while in the second phase autofluorescence was used. All of the lesions detected underwent histological analysis and the results were recorded as the number of patients with polyps. The lesions were then categorized as adenoma at different stages of dysplasia, hyperplastic polyps or inflammatory polyps. Autofluorescence described the number of patients with 'red' (adenoma) and 'green' (hyperplastic) polyps, whereas white light grouped all patients with any type of polyp together.

Positive and negative likelihood ratios (LR) were reported where possible. A positive LR is the ratio of the true-positive rate to the false-positive rate (sensitivity/(1 - specificity)). A negative LR is the ratio of the false-negative rate to the true-negative rate ((1 - sensitivity)/specificity). LRs can be interpreted as follows.

- A positive LR >10 and negative LR < 0.1 suggest convincing or definitive diagnostic evidence.
- Positive LRs of 5-10 and negative LRs of 0.1-0.2 suggest strong diagnostic evidence.
- Positive LRs of 2-5 and negative LRs of 0.5-0.2 suggest minor but possibly important diagnostic evidence.
- Positive LRs of 1-2 and negative LRs of 0.5-1 suggest generally unimportant diagnostic evidence.

a) Safety

No safety data was reported in any of the studies. It is unclear whether safety issues were not mentioned because they did not occur or because they were not the primary focus of the study. It is likely however, that because both techniques use similar instrumentation, their safety profiles would not differ significantly.

b) Effectiveness

Among the 64 patients assessed by Uedo et al. (2007), 57 polyps were detected by white light and 58 by autofluorescence; of these 28 and 26, respectively, were neoplastic. The sensitivity and specificity of autofluorescence for detecting neoplastic polyps was 84% (95% CI 71-97) and 60% (95% CI 49-71); for white light colonoscopy it was 90% (95% CI 80-100) and 64% (95% CI 53-74), respectively. The positive and negative likelihood ratios were 2.1 and 0.266, which indicate that autofluorescence provides minor but possibly important diagnostic evidence. The total number of overlooked polyps was 13 for white light (one cancerous tumour, two adenoma and 10 hyperplastic polyps) and 12 for autofluorescence (five adenoma and seven hyperplastic polyps). Typically white light missed smaller (3.6 ± 1.9 mm SD) lesions, both protruding and flat. Autofluorescence missed larger (3.9 ± 2.2 mm SD) protruding polyps, but did not fail to identify any cancerous tumours (Uedo et al. 2007).

In Brand et al. (1999), 42 abnormal lesions were detected. Histology identified 22 of the 42 lesions as adenoma, 21 as low grade dysplasia and one as high grade dysplasia. White light imaging detected 22/22 adenomas (100% sensitivity) with four false-positive findings (80% specificity). Autofluorescence found 20/22 adenoma (91% sensitivity) with two false-positive results (90% specificity). The two adenomas detected only by white light were of low grade dysplasia and showed no autofluorescence (Brand et al. 2007). The positive and negative likelihood ratios were 9.1 and 0.1, which indicate that autofluorescence provides strong diagnostic evidence. There were two incidences of false-negative readings, both with the autofluorescence imaging system. Both lesions were described by autofluorescence as normal mucosa, by white light colonoscopy as “suspicious for dysplasia” and by histopathology as low grade dysplasia (Brand et al. 1999).

Matyja et al. (2006) found that 23 of the 51 acromegalics had at least one colorectal lesion. Both white light and autofluorescence found that 11.5% (6/51) of patients had multiple pathogenic lesions with the same histology. Of the total polyps detected, 35.7% were hyperplastic, 33.9% were adenomatous, 28.6% were inflammatory and 1.8% were described as non-specific chronic colitis. Polyps were detected in 21 patients with white light imaging and 23 with autofluorescence. For the autofluorescence system, 16 'green' and seven 'red' polyps were detected. Therefore, autofluorescence had a sensitivity of 100% (23/23), while white light had a sensitivity of 91% (21/23). Because the study reported on the number of patients with polyps rather than the number of polyps detected by each system, it is hard to determine their specificity. The event of overlooking potential dysplasia was not thoroughly documented. Therefore it is only known that autofluorescence detected polyps in three more acromegalics than white light did. However, no morphological or histological data on this finding were included (Matyja et al. 2006).

None of the studies reported a statistical comparison of the results obtained for white light colonoscopy and autofluorescence imaging.

The studies conducted by Brand et al. (1999) and Matyja et al. (2006) were biased as they examined patient groups who were highly likely to have polyps, which overestimated the sensitivity of the tests. Brand et al. (1999) also introduced bias by using white light to initially identify 'suspect' areas of mucosa which required further inspection by autofluorescence. This heavily biased the results in favour of autofluorescence by overestimating its sensitivity. As well as this, two of the studies (Uedo et al. 2007; Matyja et al. 2006) looked at using autofluorescence in place of white light colonoscopy, whilst the remaining study (Brand et al. 1999) looked at using the two techniques inclusively. Ideally, a study comparing white light and autofluorescence in conjunction with white light would have been useful.

COST IMPACT

There were no cost-effectiveness studies on the use of autofluorescence colonoscopy for the detection of adenoma. Some authors have suggested, however, that the increased detection of small or flat adenomas by autofluorescence would lead to a decrease in the costs associated with the development of colorectal cancer due to overlooked pre-cancerous lesions (Rex 2006). In addition, it has been suggested that autofluorescence can reduce the cost and risk to the patient by distinguishing between threatening and non-threatening polyps, thereby ensuring that only harmful lesions are biopsied (Wang et al. 1999). The initial cost of introducing autofluorescence (including machinery, software and training) would be high, but ongoing running costs would be relatively low because of the reduced number of random biopsies required (Wang et al. 1999). According to Brand et al. (1999) the conjunctive use of autofluorescence and white light colonoscopy resulted in a longer examination time by 5-10 minutes (Brand et al. 1999). Therefore, it is necessary to determine if the purported reduction in biopsies and increased sensitivity

of autofluorescence offsets the increase in cost and time associated with its use in comparison to white light.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified from the retrieved material.

OTHER ISSUES

No issues were identified from the retrieved material.

SUMMARY OF FINDINGS

Limited evidence from one randomised and two non-randomised cross-sectional analytic studies indicated that white light colonoscopy and autofluorescence colonoscopy can detect adenoma in patients with or at risk of colorectal cancer with a similar degree of efficacy. From the available data it appeared that white light provided enhanced detection of larger protruding adenomas compared with autofluorescence, which seemed better at detecting small/flat adenomas. Thus, the two light modes used in conjunction with one another may provide the most comprehensive adenoma detection. Further studies are needed to determine if one test is superior to the other.

If the results continue to depict complimentary efficacy, further research to assess the value of autofluorescence in combination with white light colonoscopy as part of a serial testing strategy should be considered. The position of autofluorescence colonoscopy in the testing scheme would also need to be established, so that an optimal testing strategy can be identified that is both highly accurate and clinically practical. At present, there are no data documenting the clinical impact of autofluorescence imaging on the management, treatment, and outcomes of patients who are predisposed to developing colon cancer.

HEALTHPACT ACTION

Based on the very limited evidence base, autofluorescence imaging for colonoscopic adenoma detection will be monitored for 12 months.

NUMBER OF STUDIES INCLUDED

Total number of studies	3
Level III intervention evidence	3

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SEARCH CRITERIA TO BE USED

Autofluorescence colonoscopy

White light colonoscopy

Adenoma

Colorectal cancer