STUDY ID: Louwers *et al*., 2010[6]

DOMAIN 1: PATIENT SELECTION

Describe methods of patient selection: Women referred for colposcopy owing to an abnormal cervical cytology or for follow-up of a CIN1 or 2 lesion. Pregnant women, women who had been pregnant in the previous 3 months, who had had previous surgery on the cervix or pelvic radiotherapy were excluded

Was a consecutive or random sample of patients enrolled?	YES
Was a case–control design avoided?	YES
Did the study avoid inappropriate exclusions?	YES
Could the selection of patients have introduced bias?	*RISK OF BIAS: LOW*

Are there concerns that the included patients and setting do not match the review question?

APPLICABILITY CONCERNS: LOW

DOMAIN 2: INDEX TEST

Describe how the index test results were interpreted: All colposcopies were performed or supervised by expert colposcopists, according to the Dutch national colposcopy guidelines, using DySIS as a regular video colposcope. The colposcopic impression was digitally recorded by the colposcopist, with annotation of the most atypical location and predicted severity of the lesion (blinded to the DySIS analysis of the images). Once this was completed, the DySIS colour-coded map was overlaid on the image of the cervix. Test performance was determined for CIN2+, using the predetermined DySIS cut-off values used in the study by Soutter *et al*.[17] The colour-coded map was compared with the colposcopist's impression and punch biopsies were taken from all identified suspicious sites

Video colposcopy was performed using the DySIS technology, rather than conventional colposcopy (video colposcopy is rarely used in the NHS), which may have affected estimates of colposcopy accuracy. Since the model used in this study, another DySIS model has been launched (in summer 2011), designed to improve ergonomics, reduce the cost and floor print of the device (rather than resolution/accuracy)

Colposcopists had to perform at least 20 colposcopies with DySIS and supervising colposcopists at least five, before participating. All colposcopies were performed or supervised by expert colposcopists, according to the Dutch national colposcopy guidelines

Were the index test results interpreted without knowledge of the results of the reference standard?	YES
If a threshold was used, was it prespecified?	YES
Was the execution of the intervention technology as it would be in practice?	YES
Was the execution of the comparator technology as it would be in practice?	NO
Were the colposcopists undertaking the tests experienced in colposcopy (i.e. accredited and with at least 1 year's experience)?	YES

Were the colposcopists undertaking the new technologies given training/experience in the new technology? YES

Were the same clinical data available when the new technology test results were interpreted as would be available when the test is used in practice (e.g. cytology/HPV test result)? *UNCLEAR*[a]

a. [Note: Based on subsequent information from DySIS Medical, this should read 'YES'.]

Could methods used to conduct or interpret the index test have introduced bias?

DySIS RISK OF BIAS: *LOW*

COLPOSCOPY RISK OF BIAS: *LOW*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

DySIS APPLICABILITY CONCERNS: *UNCLEAR*[b]

COLPOSCOPY APPLICABILITY CONCERNS: *HIGH*

b. [Note: Based on subsequent information from DySIS Medical, this should read 'LOW'.]

DOMAIN 3: REFERENCE STANDARD

Describe the reference standard and how it was conducted and interpreted: Punch biopsies were taken from suspicious sites indicated by the colposcopist, the DySIS colour-coded map and one additional control biopsy was taken from an area of apparently normal cervical tissue on the opposite side of the lesion(s). If both the colposcopist and the DySIS colour-coded map evaluated the cervix as normal, one biopsy was taken from the transformation zone at the 12 o'clock position. No biopsies were taken if a loop electrosurgical excision procedure was performed immediately (see and treat). The biopsy sampling procedure was video recorded and later reviewed to check whether the tissue sample was collected from the annotated area. Histology reports were independently reviewed by another pathologist, with disagreements resolved by a third pathologist. The final diagnosis was determined by the majority decision

Is the reference standard likely to correctly classify the target condition? YES

Were the reference standard results interpreted without knowledge of the results of the index test? UNCLEAR[a]

Was the execution of the reference standard as it would be in practice? YES

a. (Note: Based on subsequent information from DySIS Medical, this should read 'YES'.]

Could methods used to conduct or interpret the reference standard have introduced bias?

RISK OF BIAS: *UNCLEAR*[b]

Are there concerns the target condition as defined by the reference standard does not match the question?

APPLICABILITY CONCERNS: *LOW*

b. (Note: Based on subsequent information from DySIS Medical, this should read 'LOW'.]

DOMAIN 4: FLOW AND TIMING

Draw a flow chart for the study or describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2 × 2 table: Of 275 women recruited, 36 were excluded owing to unsaved examination data (9), no colour-coded map available (9), no colposcopy undertaken after signing informed consent (3), no abnormal referral cytology (3), DSI colposcope did not start (7), no available histology (5). Therefore, the 2 × 2 table only included 239 of 275 eligible women. Although 13% of patients were excluded from the analysis, reasons for exclusion appear to be valid and not particularly biased towards either technology

Describe the time interval between index and reference standard and any actions taken: Biopsies were taken at the time of the index test, for use in the reference standard

---

Was there an appropriate interval between index test and reference standard?	YES
Did all patients receive the same reference standard?	YES
Were all patients included in the analysis?	NO

Bias: *Could the patient flow have introduced bias?*

RISK OF BIAS: *LOW*

ADDED QUALITY ASSESSMENT QUESTIONS:

1. Was a sample size calculation used? YES. A power calculation was performed; the study aimed to recruit 200 women; analyses were based on 239 women in the ITT analyses.
2. Were the data analysed by lesion, patient or both? PATIENT
3. Were results for all pre-specified outcomes reported? YES
4. Any other comments? The main concern is that video colposcopy was conducted using the DySIS equipment rather than conventional colposcopy, any differences in visualisation (e.g. owing to the different speculum) may reduce the accuracy of conventional colposcopy. In addition, it is unclear whether the same clinical data were available when test results were interpreted, as would be available in practice (e.g. cytology/HPV test result). In practice, the decision to biopsy is made using such data, in addition to colposcopic impression. [Note: Based on subsequent information from DySIS Medical, this is no longer a concern as the same clinical data were available when interpreting the results as would be available when the test is used in practice.]

STUDY ID: Soutter *et al*., 2009[17]

DOMAIN 1: PATIENT SELECTION

Describe methods of patient selection: Women referred for colposcopy owing to an abnormal cervical smear or symptoms suggesting the possibility of cervical neoplasia. Pregnant women, women who had had previous pelvic radiotherapy and women for whom any prolongation of the examination was inadvisable were excluded. In addition, women with an inadequate or inflammatory smear were excluded

Was a consecutive or random sample of patients enrolled?	YES
Was a case–control design avoided?	YES
Did the study avoid inappropriate exclusions?	YES
Could the selection of patients have introduced bias?	*RISK OF BIAS*: *LOW*

Are there concerns that the included patients and setting do not match the review question?

APPLICABILITY CONCERNS: *LOW*

DOMAIN 2: INDEX TEST

Describe how the index test results were interpreted: Areas for biopsy were marked by the DySIS user with a coloured circle. The second colposcopist completed a colposcopy form and indicated the areas for biopsy on a diagram, the DySIS pseudocolour map (PCM) and the first colposcopist's chosen biopsy points were then turned off and the second colposcopist indicated the colposcopy biopsy points on the image with a different coloured circle. The PCM was then turned back on, making both sets of biopsy points visible. The DySIS user took biopsies from all the points identified by both colposcopists. It was assumed that normal practice would include taking biopsies from lesions thought to be CIN1 and from areas with DySIS CB values of 500–552 units. Test performance was determined for high-grade CIN or invasion, using a DySIS CB cut-off value of 553 (which was determined from the data from the training group)

A precommercial DySIS model (FPC-03) was used. This has a lower resolution imaging camera than the later model used in the study by Louwers *et al*.,[6] therefore, the image resolution and accuracy are lower. Since the model used in the study by Louwers *et al*.[6] another model has been launched (in summer 2011), designed to improve ergonomics, reduce the cost and floor print of the device. In addition, the cut-off value used (to determine high-grade CIN) was determined from the data from the training group. It is unclear whether this cut-off value would be used in practice. Colposcopic assessment was performed by a second colposcopist using a video monitor displaying the images of the cervix captured by DySIS

A training group of 82 eligible women were recruited from May to July 2004, prior to the recruitment of the test group from August 2004 to July 2005

All colposcopists were experienced practitioners. UK colposcopists were accredited by the British Society for Colposcopy and Cervical Pathology and had at least 2 years' experience in busy clinics. The Greek colposcopists were similarly experienced. Most colposcopists had >5 years' experience. Both colposcopists had access to the woman's history and reason for referral

The colposcopist undertaking the colposcopy assessment used a video monitor displaying the images of the cervix captured by DySIS, so was unable to direct the colposcopic examination or request enlarged images of specific lesions (although the authors cite a publication by Ferris *et al*.,[70] which has shown that diagnostic accuracy is maintained under such conditions). Colposcopy was described as unsatisfactory in 65 cases because the squamocolumnar junction was not clearly visible, which may not have been the case if standard colposcopic equipment (with standard speculae) had been used; these patients were not excluded from the analysis. Areas for biopsy were recorded on a diagram and then transcribed on to the image, which may have introduced error. The DySIS user, rather than the colposcopist undertaking the colposcopy assessment, undertook the biopsies

Were the index test results interpreted without knowledge of the results of the reference standard?	YES
If a threshold was used, was it prespecified?	YES
Was the execution of the intervention technology as it would be in practice?	NO
Was the execution of the comparator technology as it would be in practice?	NO
Were the colposcopists undertaking the tests experienced in colposcopy (i.e. accredited and with at least 1 year's experience)?	YES
Were the colposcopists undertaking the new technologies given training/experience in the new technology?	YES
Were the same clinical data available when the new technology test results were interpreted as would be available when the test is used in practice (e.g. cytology/HPV test result)?	YES

Could methods used to conduct or interpret the index test have introduced bias?

DySIS RISK OF BIAS: *LOW*

COLPOSCOPY RISK OF BIAS: *LOW*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

DySIS APPLICABILITY CONCERNS: *HIGH*

COLPOSCOPY APPLICABILITY CONCERNS: *HIGH*

DOMAIN 3: REFERENCE STANDARD

Describe the reference standard and how it was conducted and interpreted: Both colposcopists selected areas for biopsy and also selected sites that did not seem to contain CIN in order to reduce verification bias. Histology reports were evaluated independently by another histopathologist, with disagreements resolved by a third histopathologist (16.5% biopsies were referred for a third opinion). The final diagnosis was determined by the majority opinion. Histopathologists were unaware of the DySIS result

Is the reference standard likely to correctly classify the target condition?	YES
Were the reference standard results interpreted without knowledge of the results of the index test?	YES
Was the execution of the reference standard as it would be in practice?	YES

Could methods used to conduct or interpret the reference standard have introduced bias?

RISK OF BIAS: *LOW*

Are there concerns the target condition as defined by the reference standard does not match the question?

APPLICABILITY CONCERNS: *LOW*

DOMAIN 4: FLOW AND TIMING

Draw a flow chart for the study or describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2x2 table: Of 447 women recruited to the test group, 139 were excluded owing to software problems in the initial months of the trial (15), no biopsy being taken (23), unsatisfactory view of the cervix, largely owing to the size and design of the speculae initially adapted for the instrument (45), not eligible (6), 5% acetic acid was used (1), data form lost (1), biopsy slides lost (5), blood or mucus obscuring part of the cervix (1), biopsies taken from the wrong point (3), and excessive movement preventing a reliable measurement (2), problems with the application of acetic acid, largely owing to a batch of faulty disposable nozzles (37). Therefore, the 2x2 table only included 308 of 447 eligible women

Describe the time interval between index and reference standard and any actions taken: Biopsies were taken at the time of the index test, for use in the reference standard

Was there an appropriate interval between index test and reference standard?	YES
Did all patients receive the same reference standard?	YES
Were all patients included in the analysis?	NO

Bias: *Could the patient flow have introduced bias?*

RISK OF BIAS: *HIGH*

ADDED QUALITY ASSESSMENT QUESTIONS:

1. Was a sample size calculation used? YES. A power calculation was used, based on a meta-analysis assessing the accuracy of colposcopy for diagnosing high-grade CIN; the study aimed to recruit 300 women to the test group; analyses were based on 308 women
2. Were the data analysed by lesion, patient or both? PATIENT
3. Were results for all pre-specified outcomes reported? YES
4. Any other comments? Main concerns largely stem from using a precommercial model of DySIS; a high number of eligible patients were excluded from the assessment (139/447; 31%) owing to problems with the DySIS software (15), unsatisfactory view of the cervix, largely owing to the size and design of the speculae initially adapted for the instrument (45), problems with the application of acetic acid, largely owing to a batch of faulty disposable nozzles (37), no biopsy being taken (23), biopsy slides lost (5), biopsies taken from the wrong point (3), etc. Another major concern is the use of DySIS technology for undertaking the conventional colposcopy assessment. Colposcopy was described as unsatisfactory in 65 cases because the squamocolumnar junction was not clearly visible, which may not have been the case if standard colposcopic equipment (with standard speculae) had been used; these patients were not excluded from the analysis.

STUDY ID: Flowers *et al.*, unpublished

AiC information has been removed.

STUDY ID: Gallwas *et al.*, 2011[33]

DOMAIN 1: PATIENT SELECTION

Describe methods of patient selection: Women referred for colposcopy with suspected CIN were eligible. Women aged < 18 years, and pregnant women, were excluded

Was a consecutive or random sample of patients enrolled?	UNCLEAR
Was a case–control design avoided?	YES
Did the study avoid inappropriate exclusions?	YES

Could the selection of patients have introduced bias?

RISK OF BIAS: *UNCLEAR*

Are there concerns that the included patients and setting do not match the review question?

APPLICABILITY CONCERNS: *LOW*

DOMAIN 2: INDEX TEST

Describe how the index test results were interpreted: Two investigators, blinded to the colposcopic and final histological diagnosis, evaluated each Niris image independently using a scale from 0 (normal) to 6 (squamous carcinoma). Test performance was determined for CIN1+, CIN2+ and CIN3+. Niris images were not interpreted during the colposcopic examination

Were the index test results interpreted without knowledge of the results of the reference standard?	YES
If a threshold was used, was it prespecified?	YES
Was the execution of the intervention technology as it would be in practice?	NO
Was the execution of the comparator technology as it would be in practice?	UNCLEAR
Were the colposcopists undertaking the tests experienced in colposcopy (i.e. accredited and with at least 1 year's experience)?	UNCLEAR
Were the colposcopists undertaking the new technologies given training/experience in the new technology?	UNCLEAR
Were the same clinical data available when the new technology test results were interpreted as would be available when the test is used in practice (e.g. cytology/HPV test result)?	UNCLEAR

Could methods used to conduct or interpret the index test have introduced bias?

NIRIS RISK OF BIAS: *UNCLEAR*

COLPOSCOPY RISK OF BIAS: *UNCLEAR*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

NIRIS APPLICABILITY CONCERNS: *HIGH*

COLPOSCOPY APPLICABILITY CONCERNS: *UNCLEAR*

DOMAIN 3: REFERENCE STANDARD

Describe the reference standard and how it was conducted and interpreted: It was unclear whether colposcopy results may have influenced the biopsy results, although the Niris images were anonymised

Is the reference standard likely to correctly classify the target condition?	YES
Were the reference standard results interpreted without knowledge of the results of the index test?	YES
Was the execution of the reference standard as it would be in practice?	UNCLEAR

Could methods used to conduct or interpret the reference standard have introduced bias?

RISK OF BIAS: *LOW*

Are there concerns the target condition as defined by the reference standard does not match the question?

APPLICABILITY CONCERNS: *UNCLEAR*

DOMAIN 4: FLOW AND TIMING

Draw a flow chart for the study or describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2 × 2 table: Biopsies were taken from suspicious areas only (so false-negatives would not be picked up). Analysis was performed by image (rather than by individual), and it was unclear whether all recruited patients contributed to the analysis

Describe the time interval between index and reference standard and any actions taken: Biopsy taken at time of index test for use in reference standard

Was there an appropriate interval between index test and reference standard?	YES
Did all patients receive the same reference standard?	NO
Were all patients included in the analysis?	UNCLEAR

Bias: *Could the patient flow have introduced bias?*

RISK OF BIAS: *HIGH*

ADDED QUALITY ASSESSMENT QUESTIONS:

1. Was a sample size calculation used?	UNCLEAR
2. Were the data analysed by image/lesion, patient or both?	IMAGE
3. Were results for all prespecified outcomes reported?	YES
4. Any other comments?	NO

STUDY ID: Liu *et al.*, 2010[32]

DOMAIN 1: PATIENT SELECTION

Describe methods of patient selection: Non-pregnant women ≥18 years who had abnormal cytology findings or who tested positive for hrHPV

Was a consecutive or random sample of patients enrolled?	UNCLEAR[a]
Was a case–control design avoided?	YES
Did the study avoid inappropriate exclusions?	YES

a. [Note: Based on subsequent information from Imalux Corporation, this should read 'YES'.]

Could the selection of patients have introduced bias?

RISK OF BIAS: *UNCLEAR*[b]

b. [Note: Based on subsequent information from Imalux Corporation, this should read 'LOW']

Are there concerns that the included patients and setting do not match the review question?

APPLICABILITY CONCERNS: *LOW*

DOMAIN 2: INDEX TEST

Describe how the index test results were interpreted: Results for both the Niris probe and colposcopy were recorded before performing biopsies. Test performance was determined using indeterminate and abnormal results as cut-offs for the Niris probe, and using low-grade and high-grade cut-offs for colposcopy. The cervix was divided into quadrants for examination

Were the index test results interpreted without knowledge of the results of the reference standard?	YES
If a threshold was used, was it prespecified?	YES
Was the execution of the intervention technology as it would be in practice?	NO
Was the execution of the comparator technology as it would be in practice?	YES
Were the colposcopists undertaking the tests experienced in colposcopy (i.e. accredited and with at least 1 year's experience)?	UNCLEAR[a]
Were the colposcopists undertaking the new technologies given training/experience in the new technology?	UNCLEAR[a]
Were the same clinical data available when the new technology test results were interpreted as would be available when the test is used in practice (e.g. cytology/HPV test result)?	UNCLEAR[a]

a. [Note: Based on subsequent information from Imalux Corporation, this should read 'YES'.]

Could methods used to conduct or interpret the index test have introduced bias?

NIRIS RISK OF BIAS: *UNCLEAR*[b]

COLPOSCOPY RISK OF BIAS: *UNCLEAR*[b]

b. [Note: Based on subsequent information from Imalux Corporation, this should read 'LOW'.]

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

NIRIS APPLICABILITY CONCERNS: *HIGH*

COLPOSCOPY APPLICABILITYCONCERNS: *LOW*

DOMAIN 3: REFERENCE STANDARD

Describe the reference standard and how it was conducted and interpreted: Histology results were obtained from a team of pathologists. One gynaecological pathologist served as the final reference and quality control

Is the reference standard likely to correctly classify the target condition?	YES
Were the reference standard results interpreted without knowledge of the results of the index test?	UNCLEAR[a]
Was the execution of the reference standard as it would be in practice?	YES

a. [Note: Based on subsequent information from Imalux Corporation, this should read 'YES'.]

Could methods used to conduct or interpret the reference standard have introduced bias?

RISK OF BIAS: *UNCLEAR*[b]

b. [Note: Based on subsequent information from Imalux Corporation, this should read 'LOW'.]

Are there concerns the target condition as defined by the reference standard does not match the question?

APPLICABILITY CONCERNS: *LOW*

DOMAIN 4: FLOW AND TIMING

Draw a flow chart for the study or describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2 × 2 table: Not reported (NR)

Describe the time interval between index test and reference standard and any actions taken: Biopsy taken at time of index test for use in reference standard

Was there an appropriate interval between index test and reference standard?	YES
Did all patients receive the same reference standard?	YES

Were all patients included in the analysis? UNCLEAR

Bias: *Could the patient flow have introduced bias?*

RISK OF BIAS: *UNCLEAR*

ADDED QUALITY ASSESSMENT QUESTIONS:

1. Was a sample size calculation used?	UNCLEAR
2. Were the data analysed by lesion, patient or both?	BOTH
3. Were results for all pre-specified outcomes reported?	NO. PPV and NPV results not reported
4. Any other comments?	Study conducted in China: unclear generalisability of results to a UK population.

STUDY ID: Escobar *et al.*, 2006[31]

DOMAIN 1: PATIENT SELECTION

Describe methods of patient selection: Women aged 18–80 years referred with abnormal cervical cytology (≥atypical squamous cells of undetermined significance) or with suspicious lesions of the uterine cervix were recruited. Exclusion criteria were previous hysterectomy, previous treatment for pre-invasive or invasive cervical cancer, pregnancy or being a prisoner

Was a consecutive or random sample of patients enrolled?	UNCLEAR
Was a case–control design avoided?	YES
Did the study avoid inappropriate exclusions?	YES
Could the selection of patients have introduced bias?	NO

RISK OF BIAS: *UNCLEAR*

Are there concerns that the included patients and setting do not match the review question?

APPLICABILITY CONCERNS: *LOW*

DOMAIN 2: INDEX TEST

Describe how the index test results were interpreted: Niris images were anonymised and graded as being normal, indeterminate or abnormal. No relevant details were reported for colposcopy, although observations were recorded by quadrant

Were the index test results interpreted without knowledge of the results of the reference standard?	YES
If a threshold was used, was it pre-specified?	YES
Was the execution of the intervention technology as it would be in practice?	NO
Was the execution of the comparator technology as it would be in practice?	YES
Were the colposcopists undertaking the tests experienced in colposcopy (i.e. accredited and with at least 1 year's experience)?	UNCLEAR
Were the colposcopists undertaking the new technologies given training/experience in the new technology?	UNCLEAR
Were the same clinical data available when the new technology test results were interpreted as would be available when the test is used in practice (e.g. cytology/HPV test result)?	YES

Could methods used to conduct or interpret the index test have introduced bias?

NIRIS RISK OF BIAS: *UNCLEAR*

COLPOSCOPY RISK OF BIAS: *UNCLEAR*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

NIRIS APPLICABILITY CONCERNS: *HIGH*

COLPOSCOPY APPLICABILITY CONCERNS: *LOW*

DOMAIN 3: REFERENCE STANDARD

Describe the reference standard and how it was conducted and interpreted: Biopsies were taken from each quadrant and specimens were read by one author, with a team of gynaecological pathologists serving as consultants for problem cases. Niris images were anonymised

Is the reference standard likely to correctly classify the target condition?	YES
Were the reference standard results interpreted without knowledge of the results of the index test?	YES
Was the execution of the reference standard as it would be in practice?	YES

Could methods used to conduct or interpret the reference standard have introduced bias?

RISK OF BIAS: *LOW*

Are there concerns the target condition as defined by the reference standard does not match the question?

APPLICABILITY CONCERNS: *LOW*

DOMAIN 4: FLOW AND TIMING

Draw a flow chart for the study or describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2 × 2 table: A total of 220 patients were recruited, with eight being eliminated owing to being aged < 18 years (1), heavy bleeding (2), normal cytology (1), recent cone biopsies (2), a blank form (1) and for 'unknown' reasons (1)

Biopsies were taken from each quadrant at 2, 4, 8 and 10 o'clock at the squamocolumnar junction

Describe the time interval between index and reference standard and any actions taken: Biopsy taken at time of index test for use in reference standard

Was there an appropriate interval between index test and reference standard?	YES
Did all patients receive the same reference standard?	YES
Were all patients included in the analysis?	NO

Bias: *Could the patient flow have introduced bias?*

RISK OF BIAS: *LOW*

ADDED QUALITY ASSESSMENT QUESTIONS:

1. Was a sample size calculation used?	YES
2. Were the data analysed by lesion, patient or both?	BOTH
3. Were results for all pre-specified outcomes reported?	YES
4. Any other comments?	NO