ERRATUM TO

Adjunctive colposcopy technologies for assessing suspected cervical abnormalities: a systematic review with meta-analysis and economic evaluation

The following errors in this report have been identified. Corrections are supplied in the attached pages.

1. Pages 2-3
   Author contributions, keywords word count and data sharing statement have been added to the title pages.
   Corrected pages 2-3 are copied below.

2. Pages 28-29
   Clarification that anxiety is due to incorrect test results, not the colposcopy process itself.
   Also removed suggestion that numbers of see-and-treat cases might increase.
   Corrected pages 28-29 are copied below

3. Page 35
   Clarification that no binocular colposcopy is performed alongside DYSIS video colposcopy.
   Corrected pages 35 is copied below.

4. Page 40
   Clarification that ZedScan was not included in previous assessment.
   Corrected pages 40 is copied below.

5. Pages 52-53
   Corrections to typos in column heading of Table 3 and in citation of Macdonald 2017
   Corrected pages 52-53 (Table 3) are copied below

6. Pages 54-59

   Corrections (including Table 4) to deal with incorrect assumptions on high-grade referrals in Founta (unpublished)(51)

   Corrected pages 54-59 (with Table 4) are copied below

7. Pages 88-89 (Table 16)

   Amended footnote to Table to clarify that PPV was at biopsy level in one study

   Corrected pages 87-88 (Table 16) are copied below

8. Page 199

   Removed suggestion that tests may increase anxiety.

   Also removed suggestion that numbers of see-and-treat cases might increase.

   Corrected pages 199 is copied below.

9. Page 281

   Clarified which author has an interest in Forth Photonics

   Corrected pages 281 is copied below.

Pages 2-3

Date completed (26/06/2017)

Source of funding

This report was commissioned by the NIHR HTA Programme as project number DAP35.

Declared competing interests of the authors

None

Acknowledgements

We would like to thank members of the NICE DG4 appraisal committee for providing clinical advice, including Dr Theresa Freeman-Wang, Consultant Gynaecologist, Whittington Hospital; Professor Jane Macnaughton, Professor of Medical Humanities and GP colposcopist, Durham University; and Miss Hema Nosib, Consultant in Obstetrics and Gynaecology, Hinchingbrooke Hospital. We would like to thank Dr. Pluvio Coronado from Hospital San Carlos, Spain and Matjeka Reboli, Senior Epidemiologist, Queen Mary University of London for providing additional data. We thank Mr. Philip Morgan, Health Economist at BresMed for providing assistance with the review of economic evidence.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Péron M, Llewellyn A, Moe-Byrne T, Walker S, Walton M, Harden M, Palmer S, Simmonds M. Adjunctive colposcopy technologies for assessing suspected cervical abnormalities: a systematic review with meta-analysis and economic evaluation: A Diagnostics Assessment Report. York EAG, 2017.

Contributions of authors

Mathilde Peron contributed to the protocol, performed the economic analysis and wrote all sections relating to cost-effectiveness. Alexis Llewellyn contributed to the protocol, performed the systematic review and wrote most of the sections on clinical effectiveness, Moe Byrne contributed to the protocol, performed the systematic review and wrote the background section. Simon Walker assisted the economic analyses. Matthew Walton assisted the systematic review and writing of clinical

effectiveness sections. Melissa Harden performed the database searches and maintained the review libraries. Stephen Palmer contributed to the protocol, and oversaw the conduct and writing of cost-effectiveness analyses, and the report as a whole. Mark Simmonds contributed to the protocol, performed the meta-analyses, and oversaw the conduct and writing of the clinical effectiveness sections, and the report as a whole.

Keywords

Colposcopy, DYSIS, ZedScan, Diagnostic tests, Systematic review, Economic evaluation, Meta-analysis

Word count

(main text): 49,400 words

Data sharing and accessibility

The systematic reviews in this report are all based on published material (except where provided academic in confidence). All data used is as presented in the cited references and tables and figures included in the report. Additional details on the data extracted from studies is available on request from the corresponding author. The software code for the economic model has been submitted to NICE and may additionally be requested from the corresponding author.

Please note:

Information that is provided as Academic in Confidence is highlighted in yellow. Commercial in Confidence information is highlighted in blue.

Pages 28-29

Finally, the cost-effectiveness results presented for the HPV primary screening protocols also require careful consideration. Our analysis is based on the current protocol and that the final HPV primary screening protocol may alter prior to HPV primary screening being rolled out nationally. Furthermore, key input data were derived from unpublished and preliminary results collected in the HPV pilot sites. Data collection is still ongoing and selection issues may limit the generalisability of the data used. Hence, the results under the HPV primary screening protocol should be considered exploratory and further analyses should ideally be undertaken when data collection has been completed and the implications of any selection effect is clearer.

Discussion

Extensive literature searches were conducted with an attempt to maximise retrieval of potentially relevant studies. These included electronic searches of a variety of bibliographic databases as well as screening of clinical trial registers and conference proceedings to identify unpublished studies. The search strategy did not restrict by study design. The device manufactures and study authors were contacted to provide additional data, and the review includes additional data from published studies and data from as yet unpublished studies. The review process followed recommended methods to minimise the potential for error and/or bias. The quality of the included studies was assessed and accounted for when interpreting the review results. Appropriate synthesis methods were employed by taking into account the heterogeneity of study characteristics.

Only one study of the current version of ZedScan was available, limiting the ability to compare it to colposcopy. No studies directly compared DYSIS and ZedScan. Very little data on participant subgroups was available. In particular there was little data on diagnostic accuracy in women with high-risk HPV.

There was very limited evidence relating to the clinical effectiveness of adjunctive DYSIS or ZedScan, with little reporting of any potential adverse effects.

Conclusions

The use of adjunctive DYSIS (DYSISmap with DYSIS video colposcope) increases sensitivity when compared to colposcopy alone, so it increases the number of high-grade CIN cases that are detected. However it also reduces specificity when compared to colposcopy, so more women with no or low-grade CIN will be incorrectly judged as possibly having high-grade CIN. It might therefore increase unnecessary anxiety in women with an incorrect test result. It could lead to an increase in the number

of unnecessary diagnostic biopsies, although evidence as to whether this is actually the case is limited, and complications in subsequent pregnancies in women who did not require a biopsy.

The limited evidence precludes any definitive conclusions regarding the diagnostic accuracy of ZedScan I, although it appears, like DYSIS, to increase sensitivity and decrease specificity compared to colposcopy alone, when using the currently implemented ZedScan I assessment algorithm. There is currently too little evidence to assess whether ZedScan is or is not superior to DYSIS.

The cost-effectiveness of both adjunctive technologies compared to standard colposcopy, under both the HPV triage and primary screening algorithms, appears favourable when compared against conventional thresholds used to determine value in the NHS. However, the limitations and uncertainties in the evidence base identified for ZedScan need to be carefully considered. The cost-effectiveness of both adjunctive technologies under the HPV primary screening protocol should also be reassessed when additional data becomes available from the pilot sites.

Given the limited number of studies of ZedScan, further and well-conducted diagnostic accuracy studies of ZedScan I are needed, particularly to compare its diagnostic accuracy to standard colposcopy, and in groups independent of the manufacturers. Diagnostic accuracy studies comparing DYSIS and ZedScan directly may also be useful.

As most current studies have been in women referred to colposcopy on the basis of cytology screening, diagnostic accuracy studies in women referred from HPV primary screening (or specifically in women with high-risk HPV) are needed to assess whether the new screening programme will alter diagnostic accuracy.

Study registration

The protocol for this review is registered on PROSPERO CRD42017054515

Standard binocular colposcopy, with directed biopsy/treatment when necessary, is the current usual management for people referred with abnormal cytology results. The colposcopist applies solutions such as acetic acid or Lugol's iodine, to the surface of the cervix. These help to highlight any areas of abnormality on the cervical epithelium. Video colposcopy may also be used, particularly for DYSIS where the DYSISmap is overlaid onto a video colposcopic image, and no separate binocular colposcopy will be performed.

Colposcopy involves a significant amount of subjective assessment and the final histological diagnosis depends on the training, experience, and the volume of patients seen and also the ability of the colposcopist to identify the most appropriate sites for biopsies.(24-26) (25-27) (25-27) (24) (25) (26) Details of referral cytology results, HPV status, other clinical information, the type of management available, and the number of biopsies taken may also be relevant when interpreting the results of colposcopy.

NHSCSP publication 20(15) recommends that, where a successful colposcopy has been be performed the positive predictive value to detect high-grade lesions (CIN2+) should be at least 65%. It also recommends that treatment at first visit to colposcopy should not be offered to patients referred with borderline or low-grade dyskaryosis. It also recommends that unless an excision is planned, a diagnostic biopsy should be performed when cytology results indicate high-grade dyskaryosis (moderate) or worse, and always when a recognisably atypical transformation zone is observed. In some circumstances, such as the presence of low-grade colposcopic change and high grade dyskaryosis (severe), an excisional form of biopsy (rather than punch biopsy) is recommended.

Results of biopsies are used to guide treatment decisions. Typically, areas of CIN2 or worse would usually be treated, although CIN2 may be managed more conservatively if only part of the transformation zone is affected, and in younger women who have not completed their family. Treatment options during the colposcopy examination include excising the area of abnormal cells, If an abnormality is detected during the colposcopy examination, the colposcopist may treat an abnormality during the first clinic appointment ("see and treat") by excising the area of abnormal cells where high grade changes are suspected, or in rarer cases, by destroying them in situ (ablation).(15)

The aim of excision is to remove all abnormal tissue. Excision is usually performed with a thin electrically-heated looped wire in a procedure called a large loop excision of the transformation zone (LLETZ) under local anaesthesia. The excised tissue is sent to histopathology to confirm the extent of the abnormality and inform further management. In some cases, notably where glandular abnormalities are present (CGIN), a deeper excision (cone biopsy) is required which is likely to be

3 Definition of decision problem

Women in England between the ages of 25 and 64 are invited for regular cervical screening every three to five years in order to detect abnormal cells in the cervix. Screening is conducted using liquid-based cytology; women may also be tested for high-risk human papillomavirus.

Depending on the results of the cervical screen, people may be referred for a colposcopy examination. Colposcopy is largely a subjective examination, and diagnosis will partly depend on the opinion and expertise of the colposcopist. The DYSIS digital video colposcope with DYSISmap (DYSIS Medical) and the ZedScan I device (Zilico Ltd) have been developed to be used alongside colposcopy. They aim to help the colposcopist to find abnormal cells more accurately. The DYSIS system provides a coloured map of the cervix on a computer screen, where different colours show different risks of there being abnormal cells. ZedScan uses an electrical current to distinguish between normal and abnormal cells, and shows coloured circles on a diagram ranging from green (low risk of abnormal cells) to red (high-risk).

DYSIS was previously reviewed in the DG4 assessment (30). However, additional information on this technology, development of ZedScan since that review, and recent changes in the NHS cervical screening programme mean that the relative value of using these new tests is uncertain.

This report, undertaken for the NICE Diagnostics Assessment Programme, examines the clinical and cost effectiveness of DYSISmap and ZedScan used adjunctively alongside regular colposcopy for women referred for colposcopy as part of the cervical cancer screening programme.

9.1 Decision problem in terms of PICOS and other key issues

The primary population of interest is women referred for colposcopy as part of the NHS cervical screening programme under either:

- The HPV triage screening algorithm (including test of cure), or
- The HPV primary screening algorithm as recommended for use in the sentinel sites (including test of cure).

All women who have been referred to colposcopy on the basis of a positive cytology test or because of the presence of high-risk HPV infection will be considered, bearing in mind that, outside the UK, algorithms for deciding who should be referred for colposcopy may differ from those listed above.

The tests of interest are the DYSISmap system (DYSIS Medical), which generates a coloured map representing the level of aceto-whitening of the cervix, and ZedScan I (Zilico) which uses electrical impedance spectroscopy to detect abnormal cervical tissue. Both technologies should be used

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Table 1 Overview of included studies

Study (country)	Number of full text papers	Number of conference abstracts	Publications included in the review			
			Diagnostic accuracy (full/main paper)	Other clinical outcomes (full/main paper)	Implementation (full /main paper)	Linked conference abstracts
Budithi 2016, (42) Wales	1	4	Budithi 2016 (42)	None	Budithi (2016)(43)*	Budithi (2016)(44); Budithi (2015)(45); Budithi (2015)(46)
Coronado (2016),(47) Spain	2	2	Coronado (2016)(47)	None	Coronado (2014)(48)	Coronado (2014)(49); Coronado (2013)(50)
Founta (unpublished),(51) England	1	5	Founta (unpublished) (51)	None	None	Founta (2014) (52); Founta (2014) (53); Founta (2015)(54); Founta (2015)(55); Founta (2015)(56)
Louwers (2011),(57) Netherlands	5	9	Louwers (2011)(57); Louwers (2015) (58); Zaal (2012)(59); Zaal (unpublished)(60)	Louwers (2011)(57)	Louwers (2015)(61)	Louwers (2013)(62); Louwers (2009)(63); Louwers (2010)(64); Louwers (2010)(65); Louwers (2011)(66); Louwers (2013)(67); Zaal (2012)(68); Louwers (2014)(69); Louwers (2013)(70);
Lowe (2016),(71) England	0	3	None	None	Lowe (2016)(71)*	Lowe (2016)(72) Brady (2016)(73)
Natsis (2016),(74) England	0	5	None	None	None	Natsis (2016),(74) Founta (2014)(75); Founta (2014)(76); Founta (2015)(77);

						Natsis (2015)(78)
Roensbo (2015),(79) Denmark	1	0	Roensbo (2015)(79)	None	None	None
Salter (2017),(80) USA	0	8	None	None	None	Salter (2017),(80); Salter (2016)(81); Livingston (2016)(82); Papagiannakis (2016)(83); Livingston (2016)(84); Weinberg (2017)(85); Cholkeri (2016)(86); DYSIS Medical(87)
Soutter (2009),(88) England	1	5	Soutter (2009)(88)	Soutter (2009)(88)	None	Soutter (2009)(89); Balas (2007)(90); Soutter (2007)(91); Soutter (2008)(92); Soutter (2010)(93)
Tidy (2013),(94) England & Ireland	2	7	Tidy (2013)(94); Tidy (2011)(95)	Tidy (2013)(94)	None	Tidy (2012)(96); Tidy (2011)(97); Tidy (98); Tidy (2012)(99); Tidy (2011)(100); Tidy (2011)(101); Tidy (2013)(102)
Tidy (forthcoming), (103) England	4	5	Tidy (forthcoming)(103); Macdonald (2017)(104); Palmer (2016)(105); Zilico (2013)(106)	None	Palmer (2016)(105)	Tidy unpublished(107); Macdonald (2015)(108); Tidy(109); Tidy(110); Tidy (2016)(111)
Tsetsa (2012),(112) Greece	0	3	None	None	None	Tsetsa (2012),(112) ; Tsetsa (2010)(113); Tsetsa (2011)(114)

* Conference abstract

Pages 54-59

1.1 Results: assessment of diagnostic accuracy

1.1.1 Characteristics of the included studies

Table 2 presents the summary information of characteristics of the included diagnostic accuracy studies. There were 11 studies included in the diagnostic review, including nine studies of DYSIS (42, 47, 51, 57, 74, 79, 80, 88, 112) and two studies of ZedScan.(94, 103) A total of six studies were unpublished, included three full text studies (42, 51, 103) and three studies only reported as conference abstracts.(74, 80, 112)Two studies were ongoing but reported sufficient preliminary diagnostic accuracy data to be included in this review.(74, 80) The manufacturer was involved in the design, conduct and/or interpretation of all ZedScan studies and all DYSIS studies except two.(47, 79)

All included studies were conducted in hospital-based colposcopy clinics and used a prospective cohort design. All patients underwent colposcopy with an adjunctive colposcopy technology, except for participants included in two DYSIS two-arm studies that included a separate parallel control group examined with colposcopy alone.(74, 80) Six studies were conducted in more than one centre.(42, 57, 74, 80, 88, 94)

Five studies were conducted in England.(51, 74, 88, 94, 103) Of those, one also recruited patients in Greece(88) and one involved a clinic in Ireland.(103) Other studies were conducted in Wales,(42) the Netherlands,(57) Spain,(47) Denmark,(79), the USA(80) and Greece.(112)

The sample size of studies (defined as the total number of participants analysed) ranged from 54 to 1237. Mean/median age of participants ranged from 29 to 37 years where reported. Prevalence of high-risk HPV was reported in only five studies, and ranged from 37.5% to 100%, (47, 51, 57, 74, 103) and three studies included patients with hr-HPV exclusively.(51, 74, 103)

The majority of patients included in the studies were referred to colposcopy due to an abnormal cytology/smear test, although one study only included test-of-cure patients referred with negative cytology who tested positive for hr-HPV either 6 months after LLETZ or in the context of the NHS catch-up programme.(51) All patients included in Tidy (forthcoming)(103) were referred to colposcopy through the NHS HPV-primary screening pilot.(21) A sub-study of Tidy (forthcoming)(103) included 613 patients with known-hr-HPV genotype already included in Tidy (forthcoming)(103), as well as an additional 226 (26.9%) patients, of which most (187, 82.7%) had a persistent HPV test and cytology negative result. (104) No other study included patients referred through HPV-primary screening.

Where reported, the percentage of low and high-grade referrals varied widely across the studies. Two studies study only included patients with low-grade cytology and hr-HPV.(74)(51) In other studies, between 17.1% and 52.8% of participants were referred to colposcopy with high grade dyskariosis or worse, and 9.5% to 82.9% of participants were referred with low grade dyskaryosis or less. The prevalence of histology confirmed CIN2+ varied widely, from [redacted](51) to 45.2%. Further details on histology confirmed CIN and cancer prevalence are reported in Appendix **Error! Reference source not found.**.

One study excluded women with type 3 transformation zone.(103) Five studies excluded pregnant women(42, 57, 88, 94) and two studies also excluded women with active menstruation.(94, 103) Further details on patient selection criteria and exclusions are reported in Appendix **Error! Reference source not found.**.

Of the nine DYSIS studies, all evaluated DYSISmap as an adjunct to colposcopy except one which only reported the diagnostic accuracy of DYSISmap alone against colposcopy(79) Four studies evaluated the accuracy of DYSISmap both alone and as an adjunct to colposcopy. (47, 80, 88, 104) Both ZedScan studies used ZedScan as an adjunct to colposcopy. All DYSIS studies used a DYSIS video colposcope, and both ZedScan studies used a binocular colposcope.

Six studies evaluated a commercial version of the DYSIS map, of which three used DySIS v3(42, 47, 51, 74) (80) and one used DySIS v2.1.(57) One study evaluated a pre-commercial prototype version (FPC-03)(88), and two studies did not report which version of DYSIS map was used.(79, 112) Most studies of DYSIS reported using the upper end of the acetowhitening scale of the colour-coded DySIS map to identify predicted high-grade lesions (red/yellow/white).(47, 51, 57, 80, 88) One study also included areas with weaker acetowhitening (coloured as dark blue and green, in addition to the standard red, yellow and white) as potential high-grade lesions,(79) and three studies did not report which part of the colour-coded scale was used to predict CIN2+.(42, 74, 112) Following request for information from NICE, the manufacturer stated that the DYSISmap algorithm had not changed after the FPC-03 version, and that DYSIS v3 had undergone improvements in the following areas compared with earlier versions: increased image resolution, ergonomic set-up allowing flexible positioning, working distance to allows easier biopsy and treatment, improved software usability and availability of single-use specula.

One ZedScan study was a two-phase study evaluating a pre-commercial version of the tool (3rd generation prototype);(94) in phase 1, 12 colposcopically guided ZedScan measurements were taken from the cervix: and analysed from a group of 214 people on a per-point basis to determine cut-offs for the detection of CIN2+. The cut-offs were then used in a second phase to evaluate the diagnostic

accuracy of adjunctive ZedScan with colposcopy alone, and conduct further analyses to test and determine further cut-offs.

The more recent ZedScan study, Tidy (forthcoming)(103) evaluated a commercial version of ZedScan.(103) Clarification from the manufacturer indicated that [redacted]

Table 2 Study and population characteristics

Study	Country	Sample size (N analysed)	Number of centres involved	Recruitment dates	Adjunctive technology	Age (yrs)	Hr-HPV prevalence	Reason for referral	Low grade dyskaryosis or less	High-grade dyskaryosis
Budithi 2016(42)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Coronado (2016)(47)	Spain	443	1	03/2012-02/2014	DYSIS (DySIS v3)	Mean 36, SD 10.9	37.5%*	Abnormal pap-smear	82.9%	17.1%
Founta (unpublished) DyS-CO1(51)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Louwers (2011)(57)	Netherlands	239	3	07/2008-09/2009	DYSIS (DySIS v2.1)	Mean 36.7, Median 35.3, Range 18.7-62.6	66.1%£	Abnormal cytology: 91.6% ; follow-up of untreated CIN1-2: 8.4%	66.1%	33.9%
Natsis (2016)(74) (conference abstract, ongoing study)	England Gatsehead & Taunton	287 (+948 parallel standard colposcopy control group)	2	NR	DYSIS (DySIS v3)	NR	100%	Low-grade cytology & hr-HPV	100%	0
Roensbo (2015)(79)	Denmark	239	1	12/2013-01/2014	DYSIS (version NR)	Mean 34.3, SD 11.5	NR	Abnormal cytology	NR	NR

Salter (2017)(80) (conference abstract, ongoing study, IMPROVE-COLPO)	USA	210 (+ 1788 retrospective standard colposcopy control group)~	2	NR	DYSIS (DySIS v3)	Median 31, range 21-62	NR	Abnormal cytology/pap (99%), test-of-cure (1%)	74%+	25%++
Soutter (2009)(88)	England (London), Greece	308	3	05/2004-07/2005	DYSIS (FPC-03 prototype)	Median 37, IQR 29-46	NR	Abnormal Pap test: 96.1%; symptoms 3.9%	NR	NR
Tidy (2013)(94)(phase 1)	England (Sheffield)	214 (phase 1)	2	04/2009-05/2011	ZedScan (3rd generation protoype)	Median 31.3 range 20-60	NR	Abnormal cytology	47.2%	52.8%
Tidy (2013)(94) (phase 2)	England (Sheffield), Ireland	196 (phase 2)	3	04/2009-05/2011	ZedScan (3rd generation protoype)	Median 29.5 range 20-64	NR	Abnormal cytology	56.3%	43.7%
Tidy (forthcoming)(103)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Macdonald (2017)(104) (linked to Tidy (forthcoming) (103)^	England (Sheffield)	839	1	01/2014-12/2015	ZedScan (commercial version)	Mean 32.9, range 20.3–66.1	100%	Known hr-HPV genotype (100%), abnormal cytology (73.1%),^ persistent hr-HPV/negative cytology (22.3%), follow-up (4.2%), clinical indication (0.6%)	49.0%	24.1%
Tsetsa (2012)(112) (conference abstract, unpublished completed study)	Greece	57 (54)	1	NR	DYSIS (version unknown)	NR	NR	Abnormal cytology	NR	NR

[+] LSIL, ASC-US/HPV, persistent HPV and HPV16/18; [++] HSIL, AGC and ASC-H * Low-risk HPV: 31.8%; not determined 30.7%; [#] 5.8% unknown/inadequate; [£] low-risk HPV: 30.5%; not determined: 3.3%; [redacted]
[~] details and results of retrospective arm only reported in linked separate study of LSIL and ASC-US/hrHPV(83)

Pages 88-89 (Table 16)

Table 3 Results of diagnostic accuracy studies of DYSIS included in the narrative synthesis (cut-off CIN2+)

Study	Population	N	Comparisons	Sensitivity% (95% CI)	Specificity% (95% CI)	PPV% (95% CI)*	NPV% (95% CI)*
Founta (unpublished) DyS-CO1(51)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Louwers (2015)(58), subgroup of Louwers 2011 (57)	Referral strategy 1: HPV primary with cytology triage (subgroup with a positive hrHPV test and BMD, or high-grade cytology)	165	DYSISmap+Colposcopy	81 (72-89)	64 (53-74)	71.7 (62.8-80.6)	74.2 (63.7-84.8)
			DYSISmap alone	68 (58-78)	69 (58-79)	71.4 (61.8-81.1)	65.4 (55.1-75.8)
			Colposcopy alone	53 (43-64)	82 (73-90)	77.0 (66.5-87.6)	60.6 (51.2-70.0)
	Referral strategy 2: Cytology primary with hr-HPV triage (subgroup with BMD cytology and a hrHPV positive test or high grade cytology, irrespective of the hrHPV test result)	186	DYSISmap+Colposcopy	80 (73-88)	61 (51-71)	69.0 (60.5-77.6)	74.0 (63.9-84.0)
			DYSISmap alone	65 (55-74)	69 (59-78)	69.2 (59.7-78.7)	64.2 (54.6-73.9)
			Colposcopy alone	54 (44-64)	78 (69-86)	72.2 (61.9-82.6)	60.5 (51.6-69.5)
Natsis (2016)(74)	LG cytology, hr-HPV+	287	DYSISmap+Colposcopy	82 (71.2-92.8)*	36 (29.9-42.1)*	20.9 (15.1-26.6)	90.7 (84.8-96.5)
			Colposcopy alone	27 (14.6-39.4)*	91 (87.4-94.6)*	38.2 (22.0-54.4)	85.8 (81.5-90.1)
		814	Colposcopy alone (contemporaneous control group)	36 (28.5-43.5)*	88 (85.7-90.3)*	37.1 (29.4-44.8)	87.5 (85.2-89.8)

IMPROVE-COLPO(80, 83)	Abnormal cytology/pap (99%), test-of-cure (1%) from 2 colposcopy clinics (subgroup)	210	DYSISmap+Colposcopy	83.9 (70.9-96.8)*	75.4 (69.1-81.7)*	37.1 (25.8-48.5)	96.4 (93.4-99.5)
			DYSISmap alone	74.2 (58.8-89.6)*	60.3 (53.1-67.5)*	24.7 (16.0-33.5) [@]	93.1 (88.5-97.7)
			Colposcopy	61.3 (44.1-78.4)*	91.1 (86.9-95.2)*	54.3 (37.8-70.8)[@]	93.1 (89.4-96.9)
	LG Pap smear[&] (subgroup), 44 colposcopy clinics	1857	DYSISmap+Colposcopy	NR	NR	13.3 (11.4-15.1)	NR
		1788	Colposcopy (retrospective matched control)	NR	NR	10.1 (8.4-11.7)	NR
Tsetsa (2012)(112)	Abnormal cytology	54	DYSIS+Colposcopy (3% acetic acid)	86	81	NR	NR
			DYSIS+Colposcopy (4% acetic acid)	79	77	NR	NR
			DYSIS+Colposcopy (5% acetic acid)	82	77	NR	NR

* Calculated; [@]study reported 17.1% for DYSISmap and 16.9% for colposcopy alone; PPV reported at biopsy level [&]LSIL and ASC-US/hrHPV; [+] Results for a further subgroup of 20 patients with >BMD and hrHPV negative was reported

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2 Conclusions

2.1 Implications for service provision

The use of adjunctive DYSIS (DYSISmap with DYSIS video colposcope) increases sensitivity when compared to colposcopy alone, so it increases the number of high-grade CIN cases that are detected. However it also reduces specificity when compared to colposcopy, so more women with no or low-grade CIN will be incorrectly judged as possibly having high-grade CIN. This could also lead to an increase in the number of unnecessary diagnostic biopsies, although evidence as to whether this is actually the case is limited, and to complications in subsequent pregnancies in women who did not require biopsy. The use of DYSIS is likely to be cost saving when compared to standard colposcopy.

The limited evidence precludes any definitive conclusions regarding the diagnostic accuracy of ZedScan I, [redacted] It is, therefore, also likely to be cost saving compared to standard colposcopy. There is currently too little evidence to compare the relative diagnostic accuracy of ZedScan and DYSIS.

The introduction of any of these adjunctive technologies may require additional staff training which may impose additional costs that were not considered in the analysis.

2.2 Suggested research priorities

Given the limited evidence for ZedScan, further diagnostic accuracy studies of ZedScan I are needed, particularly to compare its diagnostic accuracy to standard colposcopy, and in groups independent of the manufacturers. Diagnostic accuracy studies comparing both DYSIS and ZedScan as adjunct to colposcopy directly and against colposcopy alone may also be useful.

As most current studies have been in women referred to colposcopy on the basis of cytology screening, diagnostic accuracy studies in women referred through HPV primary screening are needed to assess whether the new screening programme will alter diagnostic accuracy.

All future diagnostic accuracy studies should have robust designs with sufficient power, including consecutive patients from a representative population of NHS referrals, ensuring adequate blinding of all assessors, and taking biopsies in all women including those with no colposcopic evidence of CIN.

Soutter (2009)(88)	Patient	Unclear protocol not found	Yes Contributed to the study design and the writing of the report. The collection and collation of the data were supervised by the principal investigator and corresponding author. The analysis of data was undertaken by the principal investigator. Corresponding author is member of the speakers bureau of Forth Photonics (manufacturer). Last author has an ownership interest in Forth Photonics	No	Yes	Unsound due exclusion of large proportion of participants (31%). Significant applicability concerns (FPC-03 prototype used)
Tidy (2013)(94)	Patient	Unclear no protocol found	Yes 1st and 2nd authors hold patents related to the technology. They are shareholders in Zilico Ltd and receive consultancy fees. Another author is also a shareholder. A 4th author is a medical advisor to Zilico Ltd and receives consultancy fees.	No	Yes	Unsound High risk of verification bias, selection bias, significant concerns about applicability (patient selection and use of pre-commercial prototype)